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A NEUROPHYSIOLOGICAL ASSESSMENT OF THE BLADDER GUARDING RESPONSE IN SPINAL CORD INJURY.

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ABSTRACT

Neuroregeneration and repair of the spinal cord following traumatic injury (SCI) provide the ultimate goal in the treatment of this patient group and in the challenge to end the permanence of paralysis. To assess the effectiveness of these techniques as they are developed it is important to have sensitive functional assessment tools capable of detecting the repair of damaged pathways. Routine assessment of SCI subjects currently relies on subjective clinical measurement using the ASIA classification and Impairment Score, which is not always consistently rated and excludes autonomic function. In eight chapters this thesis describes work executed to fill this niche by, optimising and standardizing a somatovisceral neurophysiological tool that combines the evoked potential of the sacral somatic pudendo-anal reflex response (PAR) (as a surrogate marker of the pudendo-urethral reflex) with bladder function as a measure of the integrity of the guarding response (GR) for assessing residual supra-sacral bladder and sphincter function in SCI subjects. Presented is the confirmation of the predominant absence of the GR in complete SCI and its preservation, variability and inverse correlation with the degree of impairment in iSCI. Normally suppressed during voiding, the GR is enhanced in SCI, due to aberrant sacral reflexes leading to overactivity of the bladder and dyssynergia of the sphincters. For the first time shown is the residual control of the sphincter in SCI by facilitation of the PAR that gives the best systematic correlation with ASIA grading. And the localised cortical stimulation with TMS facilitates the PAR and may provide an additional means to test the precise integrity and timing of residual cerebro-spinal pathways facilitating the guarding response and pelvic floor muscles. The relationship of this somatovisceral measure with the ASIA/IMSOP scale has been confirmed and finally discussed is how the GR, through neurophysiological testing of somatovisceral reflexes could potentially present an assessment tool for those with SCI.

ACKNOWLEDGMENTS

Serendipity put me in the path of Professor Michael Duncan Craggs who had the original idea for this project and supervised this thesis through the funding of the International Spinal Research Trust (ISRT). I thank Mike for taking me on as his PhD student, for having faith in my ability to conduct this exciting and difficult project; also for the invaluable guidance and technical assistance he gave throughout, and for always being able to put me on the right track with humour and kindness.

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Thank you, mum, dad and Kala for your never-ending faith, love and support. Lastly, thank you to the collective, for the loving guidance, the calmness and the companionship in what turned out to be the 'hermit' years.

Daddy, this is for you.

GLOSSARY

Amplitude	peak to peak amplitude of the pudendo-anal reflex response
ASIA	American Spinal Injury Association
BC	bladder capacity (mL) = amount voided/leaked/fired off+ residual volume aspirated from bladder
BN	bladder neck
CED	Cambridge Electronic Design 1401*plus* SPIKE 2 -the computer software data acquisition system
CMGs	cystometrograms
CNEMG	concentric needle electromyography
CNS	central nervous system
cSCI	complete supra-sacral spinal cord injury classified as ASIA A
Cz	vertex position on the scalp signifying the primary motor center in the precentral gyrusas measured by the intercept of tragus to tragus and inion to nasion
Digitimer	isolated constant current nerve stimulator
DPN	dorsal penile nerve stimulation, given as paired pulses: conditioning pulse is the priming initial pulse; test pulse is the 2^{nd} pulse of the paired pulse
DSD	detrusor-sphincter dyssynergia or impaired vesico-urethral function
EAS	external anal sphincter
EASEMG	external anal sphincter electromyogram
EFV	end fill volume (mL), the volume in non-SCI subjects when strong urge to void was experienced or the volume just prior to an uninhibited contraction occurred in SCI subjects
EMG	electromyogram
EUS	external urethral sphincter
GABA	≠-amino butyric acid

GR	guarding reflex, guarding response (difference explained in Chapter 1)
IMSOP	International Medical Society of Paraplegia
iEMG	integrated electromyogram
iSCI	incomplete supra-sacral spinal cord injury classified as ASIA B-D
L2	2nd lumbar vertebra
Latency	time period between the test pulse and the onset of the pudendo-anal reflex response
L region	pontine storage centre, pontine lateral nucleus, the L-nucleus- located within the pons/brainstem
LMN	lower motor neuron
LUT	lower urinary tract
M region	pontine micturition center, pontine medial nucleus, Barrington's nucleus, the M-nucleus- located within the pons/brainstem
MEP	motor evoked potential
MT	motor threshold stimulation- the DPN stimulation needed to elicit the pudendo-anal reflex response in the external anal sphincter as monitored with the anal probe
NDO or ndo	neurogenic detrusor overactivity or detrusor hyperreflexia
PAG	peri-aqueductal gray
PAR	the pudendo-anal reflex response (used as a surrogate marker of the pudendo-urethral reflex, PUR); Usually given as a mean of 10 dorsal penile nerve stimulations with standard deviations (SD) consistently ranging from 0.001-0.005. SDs have not been included in data; A ratio value arrived at by 'standardising or normalising' the mean pudendo-anal reflex response of 10 DPN stimulations to

	the pudendo-anal reflex response when the bladder is empty (PAR_{empty}); Values for the PAR are also averaged for each of the cohorts, here SDs are expressed
PAR_{efv}	pudendo-anal reflex responses at end fill volume
PAR_{void}	pudendo-anal reflex response during voiding
PAR_{ndo}	pudendo-anal reflex response during neurogenic detrusor overactivity
$PAR_{void/ndo}$	the first or the highest pudendo-anal reflex response sampled during voiding or during neurogenic detrusor overactivity
Pabd	abdominal pressure or rectal pressure
Pdet	detrusor pressure
PI	pulse interval between the test and the conditioning pulse of the paired pulses
Pves	intravesical pressure
PAR_{vc}	pudendo-anal reflex response during voluntary contraction of the pelvic floor (EAS)
Non-SCI	non-spinal cord injured subjects classified as ASIA E
NLI or X/X	Neurological level of injury indicated by most caudal normal motor vertebral level/most caudal normal sensory vertebral level; Expressed as C, cervical, T, thoracic followed by a number denoting which vertebra: C 1-5, and T 1-10
PET	positron emission tomography
p	numerical p value denoting statistical difference, with *, **, or ***
rs	Significant correlation was shown by the Spearman Correlation Coefficient

SCI	supra-sacral spinal cord injury
sEMG	surface electromyography
ST	sensory threshold- the DPN stimulation where the subject could initially feel the electrical stimulation on the dorsal penile nerve
T10	10^{th} thoracic vertebra
TMS	transcranial magnetic stimulation
UMN	upper motor neuron
VE	volitional effort
VC	voluntary contraction of the pelvic floor (EAS)
WT	working threshold - the DPN stimulation used throughout the experiment which elicited an optimal PAR response (where tolerable to the subject this was twice the motor threshold)
z	time interval (ms) between the TMS pulse and the DPN stimulation
zpp	zone of partial preservation only given for cSCI subjects
>	more than
<	less than

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Chapter 1

Introduction

1.0 Thesis Overview

In conjunction with the intent to end paralysis caused by spinal cord injury (SCI), research is being directed globally into strategies for functional restoration. These include promoting central nervous system (CNS) axon regeneration and recovery of limb function with neuro-protection after spinal cord injury (SCI) from animal models to humans (Moon and Bunge, 2005) or by tapping into cortical plasticity (Belci et al, 2004), or implanting novel devices to stimulate residual neural pathways (Grill et al, 2001; Craggs, 2004). Ultimately the aim is to develop a "cure" through functional neural repair (Ramer et al, 2005).

In order to assess the effectiveness of these techniques as they are being developed it is important to have sensitive assessment tools that are capable of detecting the repair of damaged spinal pathways. Techniques already developed for the early detection of any changes that result from neural repair (Krassioukov et al, 1999; Smith et al, 2000) are unlikely to be sufficiently sensitivity to pick up any regenerative or restorative effects of neural interventions; and the existing most commonly used spinal cord injury (SCI) assessment techniques in general verify the neurological level of injury (NLI) in terms of only motor and sensory deficits (e.g. ASIA/IMSOP Impairment Scale).

Among the SCI population recent anecdotal evidence suggests that walking is not a top priority. Interestingly a recent survey (Anderson, 2004) showed that the ability to walk was a very low priority of SCI people in the USA with only 16% (figure 1.0) regarding it to be a priority, with 44% paraplegics and 22% tetraplegics stating that bladder, bowel and sexual dysfunction was their primary concern to be resolved. Taking this fact into

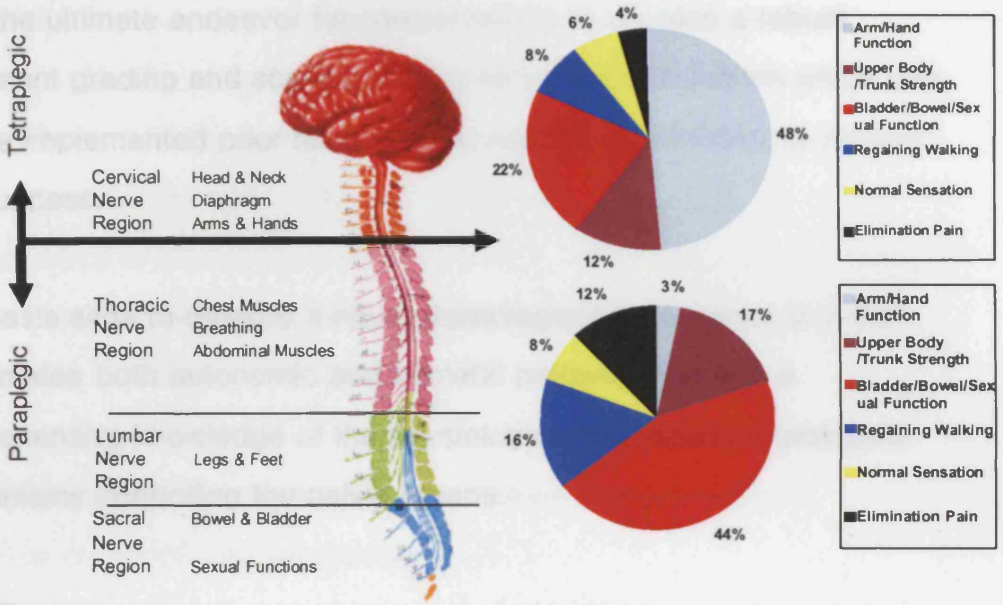


Figure 1.0 **Targeting Recovery:**
Priorities of the Spinal Cord-Injured Population – United States
[Anderson KD Journal of Neurotrauma 2004; 21(10): 1371-1383]

account it is not surprising that the emphasis on longterm care and management has been directed to sexual function and bladder and bowel management at the Spinal Research Centre, Royal National Orthopaedic Hospital NHS Trust. However current methods of assessing pelvic function have focussed on, for example, urodynamics/ cystometry and anorectal physiology which have a relatively low sensitivity and relevance to the current standards of neurological impairment testing (ASIA). With this in mind, the ultimate endeavor for researchers is to develop a robust impairment grading and scoring system for pelvic dysfunction which can then be implemented prior to, and post, neural interventions, to assess their success.

This thesis aims to develop a neurophysiological assessment tool that incorporates both autonomic and somatic pathways through a comprehensive knowledge of the physiological and neurophysiological mechanisms controlling the pelvic organs.

1.1 Background

Every year, over 1,000 people sustain a spinal cord injury (SCI), and there are thought to be 40,000 people living with SCI in the UK alone- as quoted by The Spinal Injuries Association (SIA). An injury to the spinal cord can be caused by a number of factors, from sporting activities through to disease and road traffic accidents. The majority of injuries result in paralysis, and the impact of such an injury can turn lives upside down. Individuals living with the impairment, and their families, are faced with not only the challenge of coming to terms with the injury, but also rebuilding their lives with a disability. The result of SCI is devastating and apart from the huge loss of mobility can involve major disturbances to cardiovascular and pelvic function. The impact of bladder, bowel and sexual problems on

quality of life can be detrimental necessitating long-term care and management.

Supra-sacral spinal lesions cause incontinence by interrupting descending modulatory pathways that normally coordinate bladder and sphincter function via segmental reflexes. These lesions are conventionally termed upper motor neuron lesions (UMN). Whereas lesions of the sacral cord or nerve roots, for example, cauda equina (lumbar-sacral nerve roots) damage or disease, are conventionally termed lower motor neuron (LMN) lesions. These peripheral lesions may disconnect bladder, the bowel and their respective sphincters from the spinal cord. Depending on the completeness of the lesions they often result in total loss of reflex control of the pelvic organs, again leading to serious problems of storage and voiding.

1.2 Neural control of the bladder, sphincters and pelvic floor

Peripheral innervation of the bladder

Extrinsic nerves almost exclusively control the bladder, so that contraction of its smooth muscle, the detrusor, is a coordinated event for efficient emptying. The detrusor remains quiescent at all other times whilst the bladder is filling. The bladder detrusor smooth muscle receives parasympathetic innervation from preganglionic neurons in the intermediolateral column of the S2-S4 sacral segments of the spinal cord via post-ganglionic neurons originating in ganglia of the pelvic plexus or in the bladder wall itself (Burnstock, 1990). Interacting at the peripheral ganglia are sympathetic efferent fibers of the hypogastric nerve plexus (inferior mesenteric ganglia, IMG). The sympathetic pathway has its origin in the intermediolateral column of the 9^{th} thoracic to 2^{nd} lumbar segments of the spinal cord. The preganglionic axons synapse first in the pre-vertebral ganglia or lumbosacral sympathetic chain ganglia (De Groat,

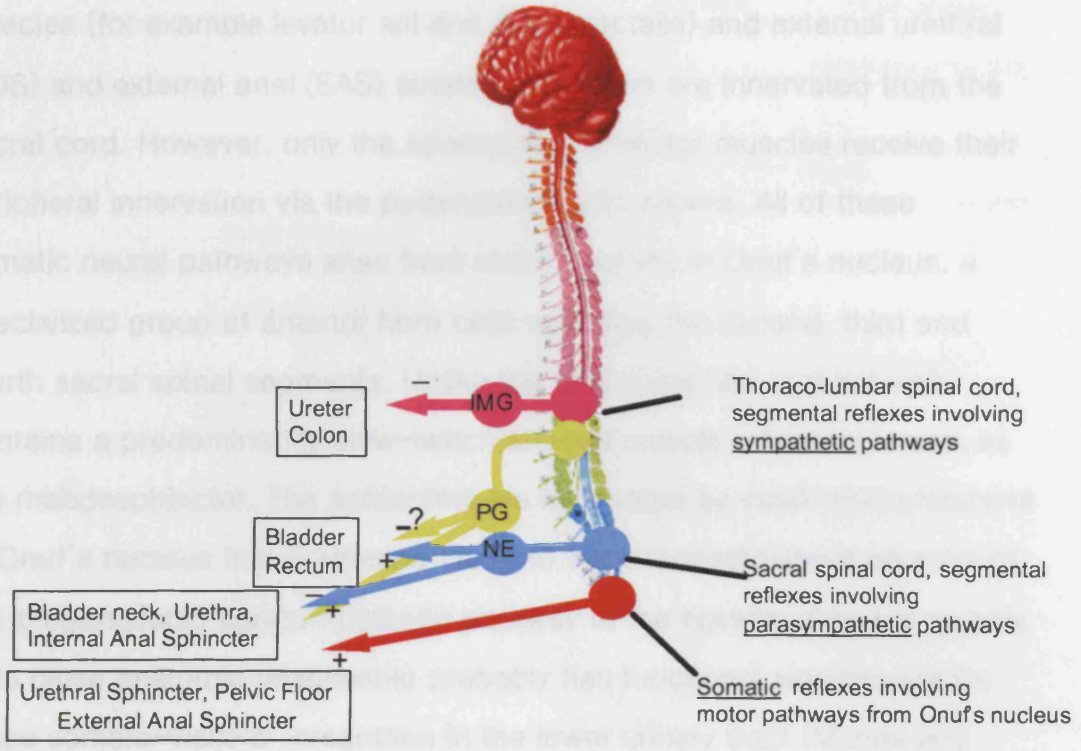


Figure 1.1 Peripheral Nerves To The Pelvic Organs
[Craggs 2006]

IMG inferior mesenteric ganglia; sympathetic hypogastric nerves;
PG peripheral ganglia- pelvic ganglia;
NE Nervi Erigentes- nerves containing preganglionic parasympathetic outflow from S2-3-4 segments.

1997) (figure 1.1).

Peripheral innervations of the pelvic floor

Muscles of the pelvic floor, including the peri-urethral and peri-anal muscles (for example levator ani and pubo-rectalis) and external urethral (EUS) and external anal (EAS) striated sphincters are innervated from the sacral cord. However, only the specialized sphincter muscles receive their peripheral innervation via the pudendal somatic nerves. All of these somatic neural pathways arise from motor neurons in Onuf's nucleus, a specialized group of anterior horn cells spanning the second, third and fourth sacral spinal segments. Unlike the anal canal, the urethral wall contains a predominantly slow-twitch striated muscle sphincter known as the rhabdosphincter. The sphincters are innervated by small motor neurons in Onuf's nucleus that is situated close to the intermediolateral neurons of the preganglionic parasympathetic pathway to the bladder detrusor muscle. This close anatomic relationship probably has functional significance for close somato-visceral integration in the lower urinary tract (Mundy and Thomas, 1994). Interestingly, unlike the EAS, the rhabdosphincter is said to have no muscle spindles and is therefore quite distinct from all other striated muscles of the pelvic floor (Schrøder and Reske-Nielsen 1983). Branches of the sacral anterior roots innervate the other muscles of the pelvic floor. Of these muscles, the levator ani group comprises a mixture of slow-twitch and fast twitch fibers that functionally provide sustained tone and phasic anti-stress contractions respectively, to give both peri-urethral and peri-anal occlusion.

The sensory pathways

Pelvic visceral nerves are the main sensory pathways from the bladder, but some sensory information is also conveyed in the sympathetic hypogastric nerves to the thoraco-lumbar spinal cord, especially from the bladder neck

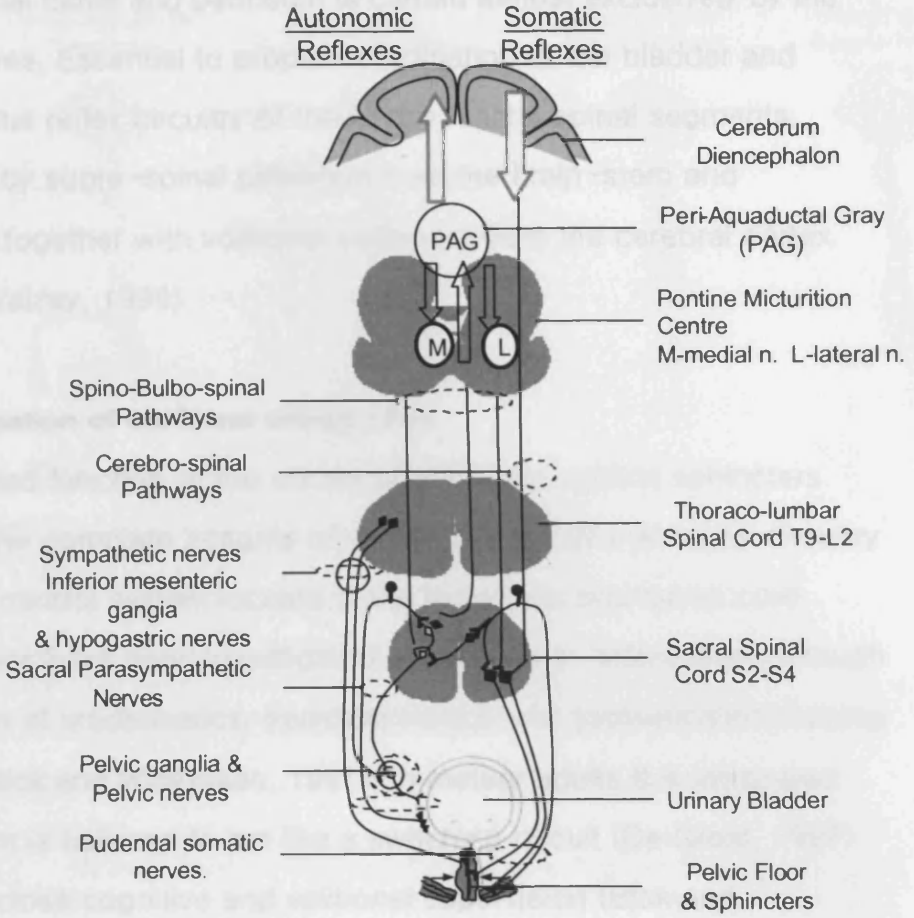


Figure 1.2 Spinal And Supra-Spinal Pathways Controlling The Lower Urinary Tract

PAG – Peri-Aqueductal Gray;
L – Lateral pontine nucleus or L-region
M – Medial pontine nucleus or M-region

[Craggs 2006]

and proximal urethra (Jänig and Morrison, 1986). Sensory information from the urethra, anal canal and perineum is carried almost exclusively by the pudendal nerves. Essential to proper coordination of the bladder and sphincters is the reflex circuitry of the lumbo-sacral spinal segments. Modulation is by supra-spinal pathways from the brain-stem and diencephalon together with volitional pathways from the cerebral cortex (Craggs and Vaizey, 1999).

1.3 Coordination of the lower urinary tract

The coordinated function of the urinary bladder and urethral sphincters depends on the complete integrity of central and peripheral neural circuitry in a complex control system located in the brainstem and spinal cord. These functions have been investigated extensively in recent times through a combination of urodynamics, neurophysiology and sophisticated imaging techniques (Blok and Willemsen, 1997). In mature adults this integrated control system is believed to act like a switching circuit (De Groat, 1997) that is under close cognitive and volitional supervision (Blok and Willemsen, 1997). Ascending afferent activity from the LUT is routed both to those parts of the brain detecting sensation and to the pontine micturition center (also known as Barrington's nucleus; M-nucleus; or M-region) through relay neurons in the peri-aqueductal gray (PAG) of the brain stem (pons). It is this M-region that appears to maintain the appropriate reciprocal relationship between lumbo-sacral reflexes so as to coordinate synergistically the bladder and the urethral sphincters during storage and voiding (Yoshimura et al, 2004) (figure 1.2).

1.4 Storage Reflexes: The Guarding Response

During bladder filling a number of lumbo-sacral reflex pathways become active, ensuring competent urethral closure together with detrusor inhibition to maintain continence (figure 1.3 this thesis focuses on B+C).

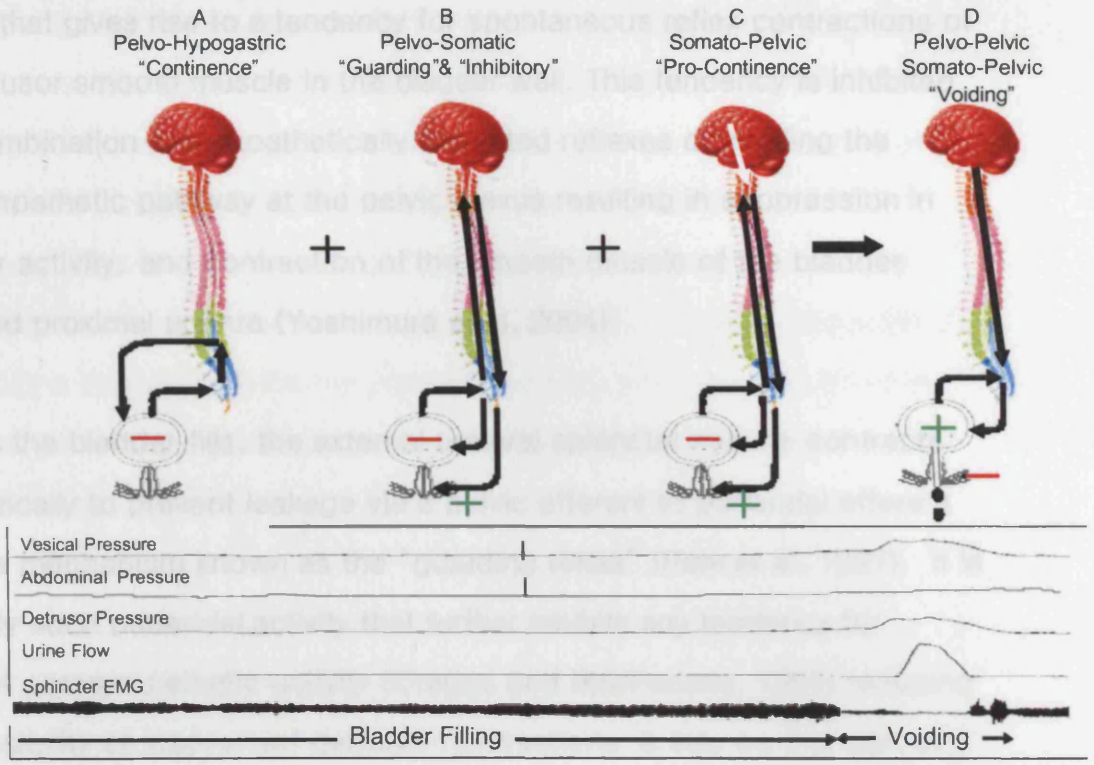


Figure 1.3 Normal Somato-Visceral Reflexes During The Micturition Cycle
Presumed progression of reflexes brought into play as the urinary bladder fills and empties. These events are recorded by combining cystometry and sphincter electromyography in the traces shown below. [Craggs 2006]

A. At the time of the first sensation of bladder filling, sympathetic inhibitory reflexes beginning to suppress the parasympathetic pathway to the bladder detrusor muscle whilst at the same time increasing tone at the bladder neck and proximal urethra to establish continence.
B. By the time of the first desire to void, the "guarding response" comes into play by increasing tone of the striated urethral sphincter automatically in response to afferent activity from the bladder. The urethral resistance increases to assist in continence. This reflex also raises the sacral segmental inhibition of the parasympathetic pathway and appears to depend upon influences of the spino-bulbar-spinal pathways via the peri-aquaductal gray and lateral pontine nucleus.
C. With sensations of a strong desire to void now taking over, the "guarding response" is operating maximally but requires the occasional additional facilitation by voluntary contractions of the sphincter to prevent inadvertent leaking of urine just before toileting.
D. At the appropriate time, the sphincters are switched "off" (probably at the pontine level) to lower urethral resistance, the bladder neck is opened, and the voiding reflex is now driven by the medial pontine nucleus. Maintenance of this sacral pelvic reflex is facilitated by a urethro-vesical reflex, promoted by urine in the urethra, to give efficient emptying of the bladder.

As the bladder fills and stores urine, there is a rising pelvic afferent nerve activity that gives rise to a tendency for spontaneous reflex contractions of the detrusor smooth muscle in the bladder wall. This tendency is inhibited by a combination of sympathetically mediated reflexes controlling the parasympathetic pathway at the pelvic plexus resulting in suppression in detrusor activity, and contraction of the smooth muscle of the bladder neck and proximal urethra (Yoshimura et al, 2004).

Thus as the bladder fills, the external urethral sphincter muscle contracts automatically to prevent leakage via a pelvic afferent to pudendal efferent reflex, a mechanism known as the "guarding reflex" (Park et al, 1997). It is probably such pudendal activity that further inhibits any tendency for aberrant parasympathetic activity (Craggs and MacFarlane, 1999) reducing the possibility of inadvertent detrusor contractions. It may be that part of the guarding reflex also involves smooth muscle responses in the bladder neck, proximal urethra and internal anal sphincter. Evidence for this mechanism is seen as a build-up in the external urethral sphincter electromyogram (EUS EMG) during bladder filling. This can be measured neurophysiologically by sacral reflexes that include the pudendo-urethral reflex (PUR) and the pudendo-anal reflex (PAR). The guarding reflex is a segmental somatic sacral reflex that is modulated viscerally by a local autonomic influence, in the form of bladder distension and supra-sacrally modulated by descending excitatory pathways some involuntary and some constituting volitional continence. Taking these modulatory factors into account an umbrella term has been given to these factors affecting continence in this thesis, namely the guarding response, for which the abbreviation, GR will be used.

1.5 Volitional Effects On Sphincter Reflexes After Spinal Cord Injury

Although most of the neural circuits involved in the normal control of the bladder are autonomic, continence is very much a function of volitional control, with voluntary contraction of the pelvic floor muscles playing an important role particularly during postponement of voiding. When the bladder achieves its near-maximal capacity at end fill volume, not only does contraction of the sphincters prevent inadvertent leaking but such contractions probably inhibit the parasympathetic reflex pathways within the spinal cord to suppress premature voiding contractions - this constitutes the volitional aspect of the GR.

This mechanism could operate directly via descending cortico-spinal pathways leading to the inhibition of sacrally mediated visceral reflexes. Indirectly there could be facilitation of the motor component of the GR that in turn activates pudendal afferents to suppress the visceral reflexes - similar to the mechanism envisaged for electrical neuromodulation (details to follow) (Craggs and McFarlane, 1999). Hence, the sensations of a full bladder and the strong desire to void can also be suppressed by voluntary contractions of the pelvic floor, or by therapeutic neuromodulation (Oliver et al, 2003).

In complete supra-sacral spinal cord injury (ASIA A) all volitional effects and sensations related to pelvic function would be expected to be lost. On the other hand, in people with incomplete lesions (ASIA B-D) the picture would be expected to be much more variable with some preservation of voluntary modulation of their pelvic floor and sphincter reflexes. It remains to be determined whether people with an incomplete spinal cord injury and some volitional control over their pelvic floor can also voluntarily inhibit NDO and suppress the desire to void.

1.6 Voiding Reflexes: Suppression / Inhibition Of The Guarding Response

Voiding, heralded by an abrupt cessation of the EUS electromyogram (EMG), is brought about by four synergistic reflexes (Yoshimura et al, 2004). Two of these cause relaxation of the bladder neck smooth muscle and EUS respectively before a third reciprocal action gives a powerful detrusor contraction, sustained by a fourth, a urethral to bladder facilitatory reflex, enabling urine to be expelled quickly and efficiently from the bladder until empty. The detrusor contraction relies on the descending drive from the M-region to the parasympathetic motorneurons in the sacral cord being turned "on" (Blok et al, 1997). Relaxation of the EUS relies on descending excitatory drive from the M-region on sacral inhibitory interneurones in the intermediomedial cell column. The inhibitory neurotransmitters involved in this pathway are ≠-amino butyric acid and glycine which inhibit sphincter motorneurones in Onuf's nucleus thereby suppressing the continuous excitatory activity from the pontine lateral nucleus (L-region or L-nucleus), thus modulating the GR and switching it off.

1.7 Spinal Cord Injury

Aberrant somato-visceral reflexes following spinal cord injury

Damage to the spino-bulbo-spinal pathways (connecting the lumbar-sacral segments with the brain-stem) in SCI, whether complete (cSCI) or incomplete (iSCI), can cause serious disruption to coordination of the pelvic organs and sphincters leading to un-inhibited pelvic (parasympathetic) reflexes. In the bladder this results in what is commonly termed detrusor hyperreflexia or neurogenic detrusor overactivity (NDO) (figure 1.4). Impaired vesico-urethral function, known as detrusor-sphincter dyssynergia (DSD), can arise from the exacerbation of NDO by uncoordinated viscero-somatic reflexes leading to obstructed voiding, high bladder pressures and incontinence (Hassouna et al 2004). Within days to

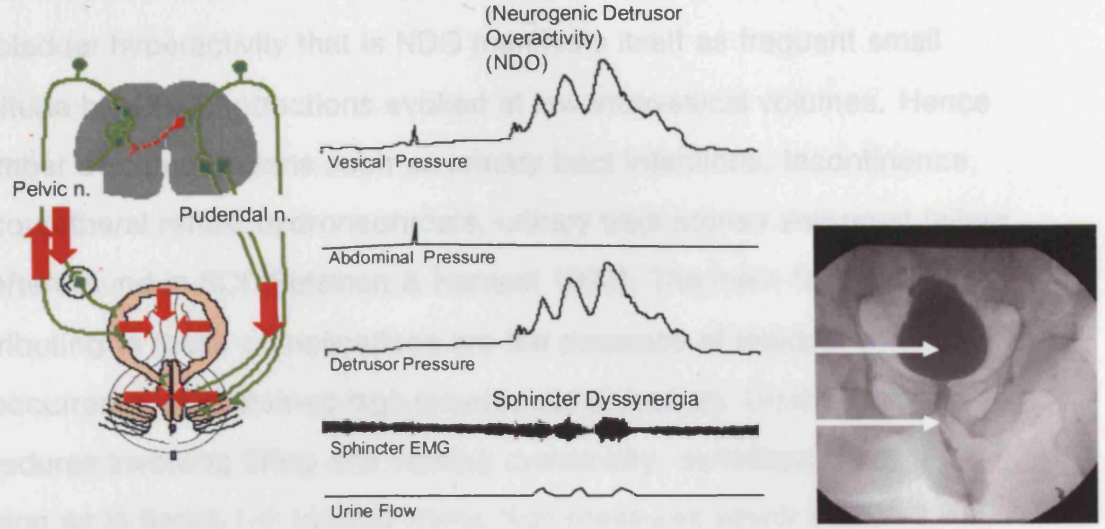


Figure 1.4 **Neurological Lesions & Urodynamic Assessment**
[Craggs 2005]

weeks of a suprasacral-SCI, the bladder smooth muscle weight increases and muscle hypertrophy occurs (aetiology not well understood). Perhaps this and the resulting changes in afferent sensory feedback contribute to the decreased compliance and hyperactivity of the bladder smooth muscle. The bladder hyperactivity that is NDO manifests itself as frequent small amplitude bladder contractions evoked at low intravesical volumes. Hence a number of complications such as urinary tract infections, incontinence, vesicouretheral reflux, hydronephrosis, urinary tract stones and renal failure are often found in SCI (Selzman & Hampel 1993). The main factors contributing to these complications are the presence of residual urine and the occurrence of sustained high intravesical pressures. Urodynamic procedures involving filling and voiding cystometry, sometimes with video-imaging as in figure 1.4, identify these high pressures which if left untreated can lead to renal failure which is an important cause of morbidity and mortality in SCI. However lower urinary tract function has a certain physiological variability. This variation and methodological inconsistency inevitably limit the reproducibility of urodynamic investigation. Different urodynamic findings may be present with a given clinical presentation, and the same urodynamic observations may be made in the presence of different symptoms Versi et al, 1991; Haeusler et al, 1995; Bergman et al, 1990; Jarvis et al, 1980; Shepherd et al, 1982; Jackson 1997).

The usual management for the neurogenic bladder is a combination of anti-cholinergic drugs to suppress the detrusor over-activity and clean intermittent self-catheterization to empty the bladder. Electrical stimulation of pudendal afferents as a treatment modality for the neurogenic bladder is an established form of therapy. Such stimulation is known to suppress bladder activity and increase bladder capacity in the SCI patient (Kirkham, *et al* 2001, Shah, *et al* 1998). Pudendal afferent stimulation can be achieved in a variety of ways, including dorsal penile (or clitoral) nerve

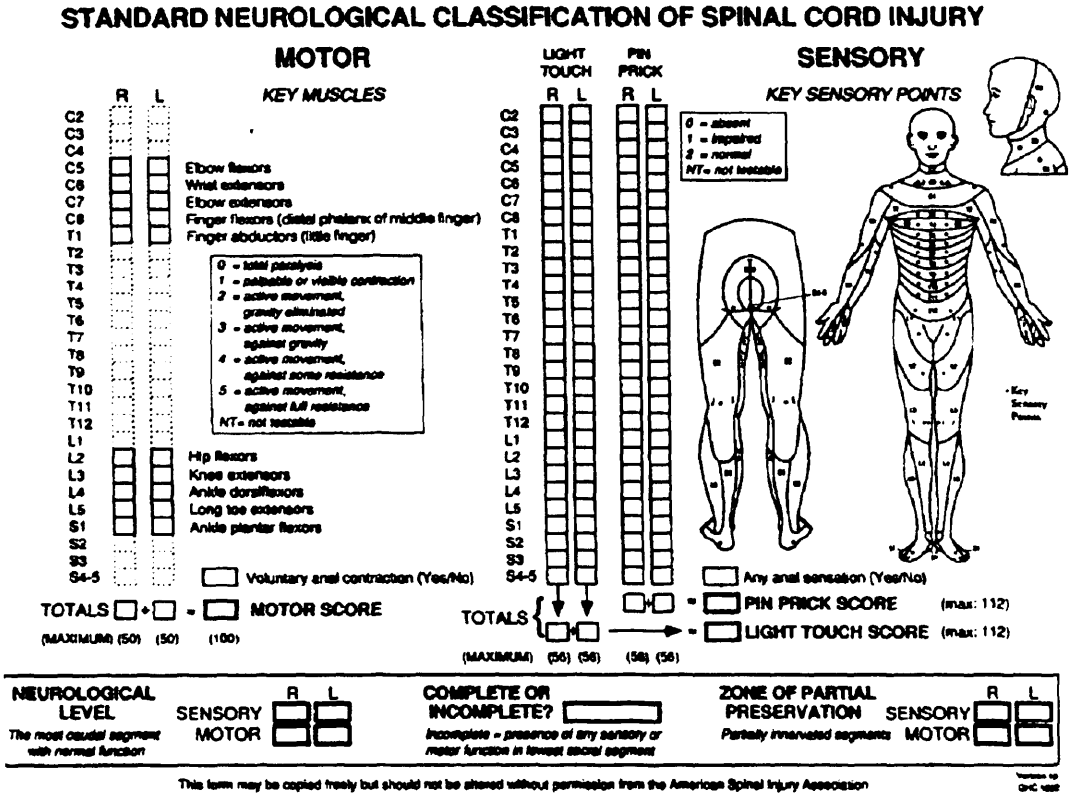
(DPN or DCN) stimulation or sacral nerve root stimulation and is also known as *neuromodulation*, defined as 'the use of activity in one neural pathway to influence the pre-existing activity in another' (Craggs & McFarlane 1999).

1.8 Assessments In Spinal Cord Injury

Functional recovery requires a multi-faceted treatment protocol. When directed at a single goal, the beneficial effects of therapy/intervention may not produce a functional return as long as accompanying problems are not resolved. If the problem of axon demyelination is left unaddressed and untreated then a treatment that increases the number of surviving axons may not subsequently promote functional recovery. In the same way it might not be enough to induce and facilitate axonal regeneration. Additionally preparation of targets of regenerated axons for synaptic connection, tuning the balance of excitation and inhibition in the target cells so that the axons can produce appropriate responses and the myelination of regenerated axons all require treatment. The chance of a single treatment pulling off this multifarious feat would be fantastic. More credible would be multiple treatments aimed at different stages and pathological processes. Accordingly assessment protocols should possess sufficient sensitivity to detect modest or even transient effects such as descent of the lesion level by a few segments. Those protocols that focus only on gross longterm outcomes or on motor recoveries may miss important intermediate effects.

1.8.1 Neurological Assessment Of Spinal Cord Injury

A good neurological examination, including both a sensory and motor examination is required to classify the level and extent of injury. While there are many different dermatome charts, it is important to utilize a chart which is widely used in the field of SCI. The International Standards for



Grade A	Complete injury	No motor or sensory function is preserved in the sacral segments S4–5.
Grade B	Incomplete injury	Sensory but not motor function is preserved below the neurological level and extends through the sacral segments S4–5.
Grade C	Incomplete injury	Motor function is preserved below the neurological level, and the majority of key muscles below the neurological level have a muscle grade less than 3.
Grade D	Incomplete injury	Motor function is preserved below the neurological level, and the majority of key muscles below the neurological level have a muscle grade 3 or greater.
Grade E	Normal	Motor and sensory function are normal.

Figure 1.5 American Spinal Injuries Association Classification Grades And Impairment Scale (1996)

Neurological classification of SCI (ASIA/IMSOP). This diagram contains the principal information about motor, sensory, and sphincter function necessary for accurate classification and scoring of acute SCI. The 10 key muscles to b tested for the motor examination are shown on the left along with the Medica Research Council grading system, and the 28 dermatomes to be tested on each side for the sensory examination are shown on the right. The system fc recording the neurological level(s), the completeness of the injury and the zone of partial preservation (in complete injuries) are shown at the bottom.

Neurological and Functional Classification of Spinal Injury (revised 1996- adapted from an original classification scheme by Frankel et al 1969), endorsed by both the American Spinal Injury Association (ASIA) and the International Medical Society of Paraplegia (IMSOP) is recommended and classes a spinal cord injury as "A, B, C or D, with normal motor and sensory function being classified "Grade E" (Figure 1.5). This ASIA/IMSOP classification system gives little direct indication of the neurology associated with autonomic dysfunction but clearly there must be some relationship when somato-visceral reflexes are aberrant, as occurs in SCI. The neurological examination is often held as the golden standard against which all other tests of function have to be measured. However several drawbacks exist such as patient co-operation requirement, latency and amplitude of changes of responses within the central nervous system cannot be readily assessed, and there is inherent subjectivity in the observations, as well as variability between examiners, which decrease the reliability of detecting small changes (Young and Mayer 1986). Although more recent somato-sensory (Krassioukov et al, 1999) and somato-motor (Smith et al, 2000) testing is introducing more objective neurophysiological measures into the evaluation of people with iSCI, these are unlikely to have the sensitivity to pick up any regenerative or restorative effects of neural interventions.

1.8.2 Neurophysiological Measures Of Sacral Reflexes

Neurophysiological testing of sensory and motor function can be used to assess neurological deficits. Routine clinical neurophysiological testing of pelvic floor or sphincter muscles can be done by directly examining various sacral reflexes involving the bulbocavernosus, ischiocavernosus or sphincter muscles. Diagnostically, examination of these reflexes by concentric needle electromyography or, with surface electrodes, is advocated for all people presenting with sacral dysfunction (Fowler et al,

2002). The term complete lesion is commonly used when there is an absence of somatosensory and motor function in the lowest sacral segments. The term incomplete lesion is used when there is a preservation of perineal sensation to light touch and the voluntary contraction of the external anal sphincter (EAS). Investigating the sacral reflexes will theoretically inform about the preservation or damage of the lower spinal cord and thereby the innervation of bladder and external urethral sphincter (EUS) (Wyndaele, 1997). Electromyographical studies can provide quantitative data concerning segmental reflexes, long loop pathways and descending motor pathways and have been extensively used. Evoked potential studies can yield reliable data concerning electrical manifestations of responses conducted through the spinal cord- in the pathways being stimulated, thus demonstrating conduction in patients with no apparent function.

1.8.3 Sacral Reflexes: Pudendo - Urethral And Pudendo -Anal Reflexes

The pudendal nerve leaves the pelvis through the lower part of the greater sciatic notch beneath the lower border of the piriformis muscle. It bifurcates just before the sacrospinal ligament, with one branch going to the EAS and the other to the EUS. The motorneurones for both the external anal and urethral sphincters are sited close together in Onuf's nucleus in humans, which is in contrast to most other non-primate animals (figure 1.6 Blok, 2002). Application of electrical stimulation of pudendal afferent nerves can be applied via the dorsal penile nerve (DPN) in men or the dorsal clitoral nerve (DCN) in women thereby eliciting the PUR and the PAR responses (figure 1.7A). There is considerable evidence showing that the behaviour of these two reflexes 'mirror one another (Podnar and Vodusek, 2001). At the Spinal Research Centre, RNOH NHS Trust, Stanmore, the DPN stimulation technique is of long-standing. It has been shown here in non-SCI subjects that DPN stimulation elicits an increase in EUS activity,

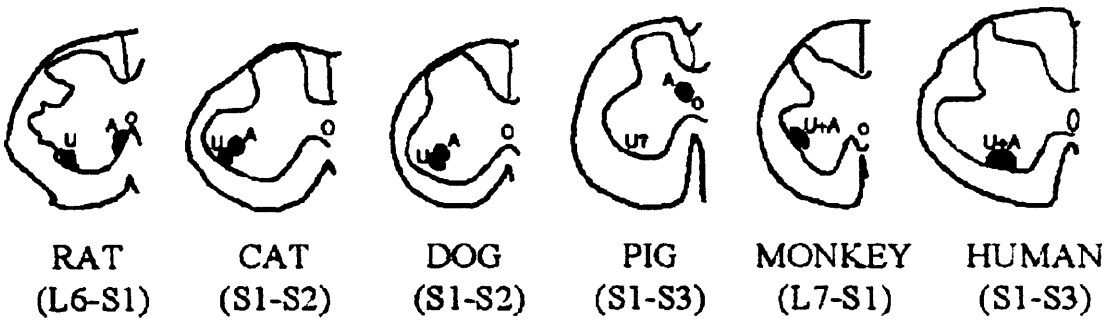


Figure 1.6 Onuf's Nuclues

Location of the Onuf's nucleus is shown for the external urethral (U) and anal (A) sphincters in several species, including humans

[Blok 2002]

which is accompanied by EAS activity, resulting in the interruption of urine flow (figure 1.7B). This mirroring has been demonstrated in SCI subjects during periods of DSD and during DPN stimulation (Zafirakis, 2002).

The use of the EAS as a signal source for EMG measurement in urodynamic studies of bladder function has been proved to be a reliable means of evaluating EUS activity in patients in other laboratories too (Barrett, 1980; Perkash, 1980; Vereecken and Verduyn, 1970). This has also been confirmed in animal studies and is due to relaxation of both the EUS and the EAS in response to a detrusor contraction (Bradley and Teague, 1972 (cats); Tomohiko et al, 1982) and more recently by Wenzel (2006) who detected neurogenic detrusor contractions from the activity of the external anal sphincter in cat and human.

1.8.4 Surface electromyography versus fine wire electromyography

Electromyography (EMG) of the EUS was first performed by Petersen and Franksson in 1955 using concentric needle electromyography (CNEMG). In general, invasive fine wire electrodes are used most commonly for diagnosing inappropriate EAS activity during dynamic studies. However Binnie et al. (1991) showed good correlation between EASEMG data obtained using invasive fine wire stainless steel electrodes and data obtained using the non-invasive longitudinal electrode anal plug; and also that an anal plug electrode with longitudinal electrode plates, rather than the traditional circumferential electrode plates, significantly improved the detection of the EAS EMG signal response on eliciting the evoked PAR response.

1.8.5 Sphincter activity as the Key to the Guarding Response

Park *et al.* (1997) suggested that the key to bladder control may lie in the assessment of the external urethral sphincter (EUS) which is the result of

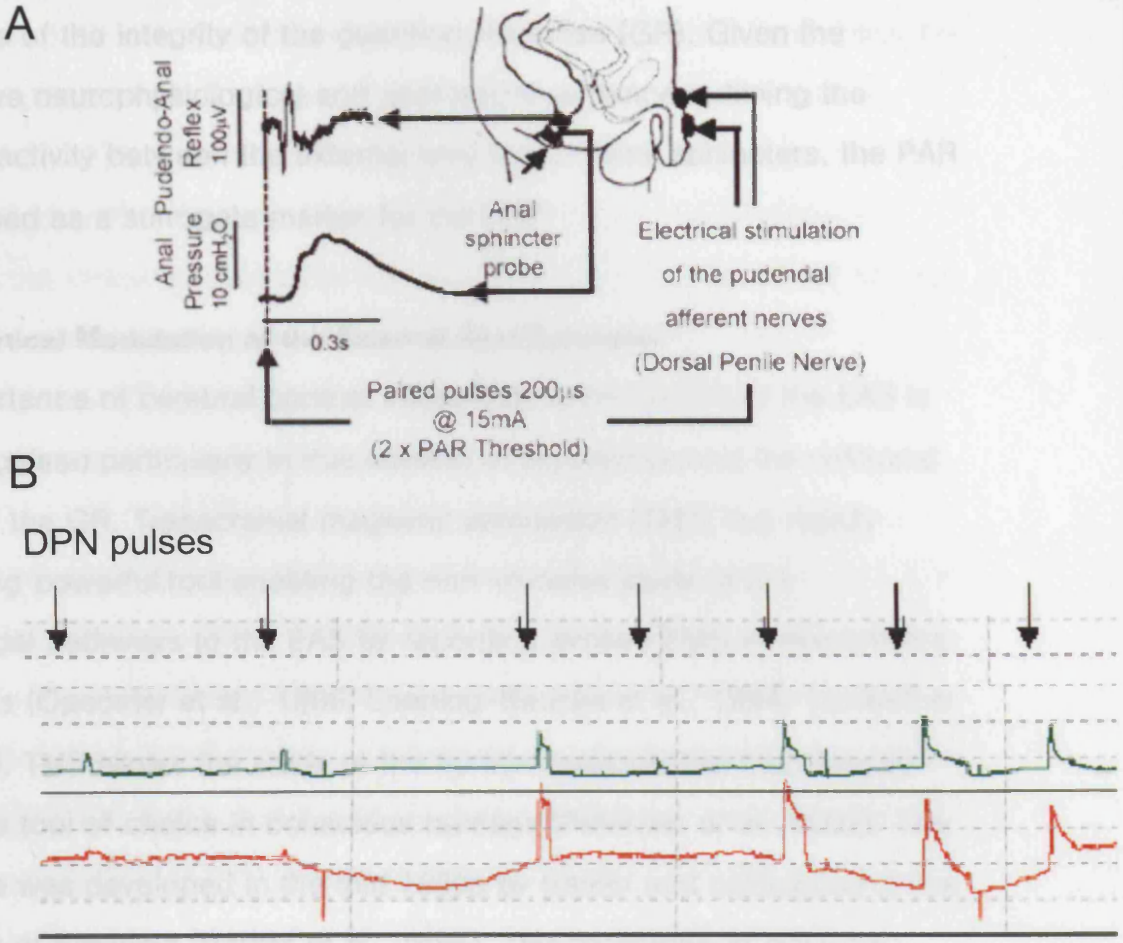


Figure 1.7 Elicitation Of The PAR Response And Mirroring Between The EU And EAS Activity With DPN Stimulation

A. Evoking the reflex by selective pudendal afferent nerve stimulation the dorsal penile (or dorsal clitoral) nerves.
B. Sample recordings in a non-SCI subject
C.

The black arrows indicate times of DPN stimulation. The top green trace shows EUS pressure; the red trace is the intra-anal pressure changes. An increase in urethral pressure that is mirrored by an increase in intra-anal pressure was seen occur at each period of DPN.

voluntary somatic neuromuscular control and involuntary autonomic regulation. Thus the pudendo-urethral reflex (PUR) response may provide a measure of the integrity of the guarding response (GR). Given the substantive neurophysiological and anatomical evidence outlining the matched activity between the external anal and urethral sphincters, the PAR can be used as a surrogate marker for the PUR.

1.8.6 Cortical Modulation of the External Anal Sphincter

The importance of cerebral cortical influences in the control of the EAS is well recognised particularly in this context of continence and the volitional aspect of the GR. Transcranial magnetic stimulation (TMS) is a rapidly developing powerful tool enabling the non-invasive study of the corticofugal pathways to the EAS by recording evoked EMG or manometric responses (Opsomer et al., 1989; Loening-Baucke et al., 1994; Turnbull et al., 1994). TMS allows the study of the human corticospinal tract function and is the tool of choice in conscious humans (Petersen *et al.*, 2003). The technique was developed in the mid 1980s by Barker and colleagues at the University of Sheffield (Barker *et al.*, 1985). This technique of inducing current in the brain is based on the phenomenon of electromagnetic induction whereby TMS preferentially excites those inter-neuronal axons that lie parallel to the surface of the coil in the brain which in turn influence the corticospinal neurons. TMS does not stimulate unmyelinated and A delta nerve axons or endings in the scalp or meninges thus rendering it a painless technique.

The TMS machine consists of large capacitors which may be discharged rapidly sending a brief current through a coil. This in turn induces a transient magnetic field (1.5 - 2 Tesla maximum) inducing a current in the neurons in the brain. The induced current diminishes with increasing depth and halves at about 4 cm from the coil surface. There are 3 basic coil

shapes: circular, figure-of-8 and angled double cone coil. Depending on the size, shape of coil and the pulse output from the machine (monophasic and biphasic) the site of stimulation could be non-focal (circular), focal on the surface (figure-of-8) or deep focal (angled double cone) (Terao & Ugawa, 2002). The deep focal angled double cone coil (Hamdy *et al.* 1998) is used in EAS EMG studies. TMS elicits an excitatory response, known as the motor evoked potential (MEP), which is usually a biphasic or a compound response in the electromyographic recording-depending on the target muscle. When a muscle is voluntarily contracted, the MEP in response to TMS is facilitated- and more easily identified.

In SCI, although there are deficits associated with the lesion, there are also changes elsewhere in the CNS, both in the brain and in the spinal cord. One of the characteristics of the human motor cortex is plasticity; cortical excitability can be modified by injury thereby reorganizing motor control. The circuits in the motor cortex can be either excitatory or inhibitory in their influence on cortical output. The output from motor cortex to muscles is predominantly via the crossed corticospinal tract, although a small proportion of fibers descend via uncrossed pathways. Cortical output is also influenced by interactions between the two hemispheres. Reorganisation of motor control takes place in the cortical circuits as a result of spinal cord injury. Little is known about cortical pathways of autonomic function and the cortical reorganisation, following injury, influencing the motor and autonomic output from the brain. The accumulation of more knowledge in this area will help determine recovery strategies following injury and thereby improve interventions aimed at rehabilitation.

Chapter 2

Study Design And Chapter Outline

2.0 Study Design

Techniques already developed for the early detection of any changes that result from neural repair (Krassioukov et al, 1999; Smith et al, 2000) are unlikely to be sufficiently sensitivity to pick up any regenerative or restorative effects of neural interventions; and the existing most commonly used spinal cord injury (SCI) assessment techniques in general verify the neurological level of injury (NLI) in terms of only motor and sensory deficits (e.g. ASIA/IMSOP Impairment Scale). A recent survey (Anderson, 2004) has shown that neural repair of pelvic function is a top priority for a large percentage of SCI people in the USA. Current methods of assessing pelvic function have focussed on, procedures (for example, urodynamics/ cystometry and anorectal physiology) which have a relatively low sensitivity and relevance to the current standards of neurological impairment testing (ASIA). With this in mind, the ultimate endeavor for those researchers will be to develop a robust impairment grading and scoring system for pelvic dysfunction which can then be implemented prior to, and post, neural interventions, to assess their success.

Routine clinical neurophysiological testing of pelvic floor or sphincter muscles can be done by directly examining various sacral reflexes involving the sphincter muscles, theoretically giving information about the preservation or damage of the lower spinal cord and thereby the innervation of bladder and EUS (Wyndaele, 1997). Electromyographical studies can provide quantitative data concerning segmental reflexes, long loop pathways and descending motor pathways. Evoked potential studies can yield reliable data concerning electrical manifestations of responses

conducted through the spinal cord- in the pathways being stimulated, thus demonstrating conduction in patients with no apparent function.

Park *et al.* (1997) suggested that the key to bladder control may lie in the assessment of the external urethral sphincter (EUS) which is the result of voluntary somatic neuromuscular control and involuntary autonomic regulation. The sacral reflexes, the pudendo-urethral reflex (PUR) response, and the pudendo-anal reflex (PAR), when elicited by dorsal penile nerve (DPN) stimulation, result in a short-lived contraction of the EUS, and the external anal sphincter (EAS). These reflexes may provide a measure of the integrity of the guarding response (GR).

The overall thesis hypothesis: 'the guarding response (GR) can be used as a sensitive measure for evaluating functional restoration in spinal cord injury (SCI)' was broken down into several experimental hypotheses. The first of these '*the PAR can be used as a measure of the integrity of the guarding response*' was addressed in the first experimental chapter (chapter 3) the aim of which was to establish the pudendo-anal reflex (PAR) neurophysiological tool as a marker of the involuntary aspect of the guarding response (GR). To do this the evoked PAR was researched during different bladder states in both non-SCI and spinally injured subjects: when the bladder was empty, at end fill volume (when GR was maximal in non-SCI subjects). Chapter 4 investigated the behaviour of the GR during voiding or neurogenic detrusor overactivity (NDO) in those with spinal injury (SCI).

As discussed the maintenance of continence incorporates an essential volitional aspect- which is the modulatory role to the GR. This element gave rise to the following experimental hypotheses in the thesis: '*modulation of the GR by volitional effort is not the same in non-SCI and*

SCI subjects; the sensitivity of the techniques of integrated EMG (iEMG) and evoked-PAR in assessing voluntary effort is not the same. Therein chapter 5 addressed these two hypotheses, aiming to investigate the descending modulatory pathways, by evoking the PAR when subjects were asked to contract or imagine contracting their pelvic floor or sphincters and comparing the traditional method of assessment (iEMG) with the method presented in this thesis.

Furthermore, the potential for utilising preserved voluntary pathways in SCI may well help to restore normal function by facilitating sacral reflexes such as the PAR gave rise to a further experimental hypothesis: '*the modulatory effect of TMS on the PAR is independent of the timing of its application*'. Thus chapter 6 contains a preliminary study to investigate the relationship between the activation of cortico-spinal pathways by looking at the modulatory impact of transcranial magnetic stimulation (TMS) on the PAR response in people with and without incomplete spinal cord injuries. Using statistical analysis, the final hypothesis: *the PAR response is related to the current neurological gold standard assessment tool used in SCI*, is tackled in chapter 7.

Data Analysis

PAR data was processed and analysed using the Spike program. All information was treated confidentially and conformed to the regulations described in the Data Protection Act. All PAR values underwent a process of standardisation or normalisation. This term refers to all PAR values elicited in one subject being ratioed (divided by) to the PAR of the empty bladder (such that the normalised PAR value for the empty bladder in each subject was always equal to 1). All data was pooled and expressed as a mean ± SD. Statistical analysis was performed using Prism 4.0 statistical package. Clinical statistical significance between SCI and non-SCI subject

data was determined with 95% confidence interval using an unpaired 2-tailed t-test with Welch's correction. [The unpaired t test assumes that the two populations have the same variances. Since the variance equals the standard deviation squared, this means that the populations have the same standard deviation). A modification of the t test (developed by Welch) is used when one is unwilling to make that assumption]. Correlation studies used the nonparametric Spearman correlation coefficient, rs which made no assumption about the distribution of the values, as the calculations are based on ranks, not the actual values. Correlation reported numerical results (rs, 95% CI of rs, p-value testing the null hypothesis that r is really zero). The repeatability of the technique was assessed with the aid of Dr Richard Morris, the UCL employed statistician using intra subject correlations (also known in the statistical literature as intra-class correlations, (ICCs)). It equals the ratio of between subject variance to (between subject variance plus within subject variance). A higher ICC value (closer to 1), was associated with greater repeatability of the parameter.

2.1 Outline Of Thesis

Chapter 1 Overview and Introduction of the thesis

This chapter addresses the clinical problem that pelvic dysfunction is a top priority for those with SCI, and with functional neural repair research taking off there is a vast niche in the assessment milieu for a neurophysiological tool that incorporates somatovesical pathway assessments. The chapter then goes on to describe pelvic function in non-SCI subjects accenting the role of the guarding response (GR), with both its involuntary and voluntary aspects. This is followed by the changes brought about by SCI and the emergence of aberrant reflexes in relation to the GR. Then a

description of current assessments of SCI that exist going on to illustrate their limitations and the need for a development and modification of existing procedures into an adequate tool of assessment.

Chapter 2 Study Design and Thesis Outline

This chapter summarises what is known and unknown in the research and the hypotheses that form the basis of the thesis with the research formula employed therein.

Chapter 3-6 are clinical experiments

Chapter 3 Modulation of the bladder guarding response during filling cystometry

This chapter aimed to optimise, standardise and confirm the technique of evoking the pudendo-anal reflex response (PAR) by dorsal penile nerve stimulation (DPN), as a measure of the GR in non-SCI and SCI subjects, and to test the repeatability of the measure.

Chapter 4 Modulation of the bladder guarding response during voiding cystometry

This chapter aimed to optimise, standardise and confirm the technique described for chapter 3 to investigate the level of suppression or inhibition of the GR during voiding in non-SCI and SCI subjects and to test the repeatability of the measure. Voiding in the SCI subjects being indicative of the leaking also known as 'firing off' that takes place during neurogenic detrusor overactivity (NDO) and detrusor sphincter dyssynergia (DSD).

Chapter 5 Supra-spinal modulation of the guarding response during voluntary effort

This chapter aimed to investigate the modulation of descending pathways on the pudendo-anal reflex response when the subject is asked to contract or squeeze their pelvic floor. This was investigated in non-SCI and SCI subjects. Descending pathways and residual volitional pathways were assessed also using the more traditional methods of integrated EMG (iEMG) which was compared to the modulation of the evoked sacral reflex technique.

Chapter 6 Modulation of the bladder guarding response by transcranial magnetic stimulation

This chapter aimed to investigate the modulation of the evoked pudendo-anal reflex response by transcranial magnetic stimulation (TMS), using the TMS pulse as a conditioning and test pulse with respect to the DPN stimulation and varying the interstimulus interval therein, such that the excitatory and inhibitory nature of supra-sacral modulation could be further established.

Chapter 7 Relationship between the guarding response and standard neurological assessment

This chapter investigated the correlation of the evoked pudendo-anal reflex measure when modulated by the different elements described in the previous chapters (3 to 6) with the currently most common neurological assessment tool used today in spinal cord injury, with the intention to better able gauge its niche in the current assessment technique milieu.

Brief discussions of the results are included at the end of each chapter.

Chapter 8 General Discussion, criticisms and Future Work

The analyses of the experimental results are brought together and discussed, to give a balanced preliminary evaluation of the pudendo-anal reflex response, a measure of the guarding response, as a neurophysiological assessment tool of SCI recommending future work to get an insight into its potential role in neural functional repair studies.

Chapter 3

Modulation Of The Bladder Guarding Response During Filling Cystometry

3.0 Introduction

Neuroregeneration and repair of the spinal cord following traumatic injury provide the ultimate goal in the treatment of this patient group. However, in order to assess the effectiveness of these techniques as they are developed it is important to have sensitive functional assessment tools that are capable of detecting the repair of damaged pathways. Most techniques already developed for the early detection of any changes that result from neural repair do not consider autonomic and somatic pathways such as those existing for the bladder.

The micturition cycle is a primary function of the lower urinary tract, which requires the synergistic action of two muscular structures, the urinary bladder and the urethra with its sphincters. This coordination is dependent upon the integrity of neural pathways connecting the brainstem (the pons) and higher centres to the lumbosacral spinal cord. It has been shown that the area responsible for the synergistic action of both detrusor and urethral closure mechanism is located in the brainstem (Blaivas 1982, Chancellor *et al.* 1990) - this is the area of synthesis of the guarding response (GR). Thus normal coordination and control of the bladder and urinary sphincters is dependent upon the complex interaction of signals arising from the pons and their effect on local segmental reflexes in the sacral spinal cord. The GR refers to the progressive involuntary increase in the activity of the external urethral sphincter (EUS) during bladder filling which switches to a conscious voluntary phenomenon at higher bladder volumes (Park *et al.* 1997), from this it was suggested that it is the GR that prevents the bladders natural propensity to contract at low volumes in healthy individuals thus maintaining continence. The activity of the external anal

sphincter (EAS) was used as a surrogate for the EUS for reasons previously discussed in Chapter 1, such that the status of the EAS may give a sensitive representative measure of the integrity of the GR. Damage to the spinal cord can lead to impaired bladder and sphincter function and the emergence of aberrant reflex activity seriously marring the integrity of the GR, after the initial 'spinal shock' phase (de Groat *et al.* 1997) causing detrusor–sphincter dyssynergia, (DSD) and neurogenic detrusor overactivity, (NDO/ndo, also previously known as detrusor hyperreflexia). These changes are accompanied by sustained high bladder pressures and small bladder capacities, appear to long lasting and irreversible and may seriously confound the effectiveness of successful restoration of normal central nervous system output to the lower urinary tract.

3.0.1 Dorsal Penile Nerve Stimulation

This study uses dorsal penile nerve stimulation (DPN) which is a very well tolerated and established technique shown to suppress reflex detrusor contractions in SCI patients (Shah *et al* 1998; Kirkham *et al* 2001) by applying electrical stimulation to pudendal afferent nerves to stimulate bilaterally a fraction of the first to third posterior sacral nerve roots. This produces reflex contraction of the muscles which are innervated by the pudendal nerve, namely, the external anal (pudendo-anal reflex response, PAR) and external urethral (pudendo-urethral reflex response, PUR) sphincters, the pelvic floor musculature and the bulbocavernosus muscle, by which to assess the integrity of the GR. For the purposes of the study presented in this thesis a control group of non-SCI male subjects would find EUS CNEMG an uncomfortable procedure. In order to minimise any potential discomfort in non-SCI and iSCI subjects the assessment of the PAR was chosen as a surrogate marker for the PUR.

3.0.2 Urodynamic Assessment Of Pelvic Dysfunction

Pelvic performance is assessed by standard subtraction cystometry during serial cystometrograms. Standard subtraction cystometry is the subtraction of the abdominal pressure from the intravesical pressure resulting in an absolute value for detrusor pressure. This involves rectal pressure monitoring which gives abdominal pressures.

However there are reported disadvantages of rectal pressure monitoring including poor pressure recordings because of low or inappropriate insertion of rectal catheter, the contact of the rectal transducer to rectal walls or faeces, rectal motility and contractions (Abdel-Rahman, 1982, McCarthy 1982, Bhatia and Bergman, 1986, James et al 1987, Dmochowski, 1996). All of which Ersoz and Akyuz (2004) suggest are more prominent in SCI subjects because of the increased reflex activity giving rise to the higher possibility of inconsistent results in this patient group. For this reason derived detrusor pressure is considered less important during cystometry of SCI patients than it is in the neurologically intact population. For this reason in this study only intravesical pressure (Pves) was monitored and used to predict the onset of neurogenic detrusor overactivity in spinal injured subjects.

3.1 Aim

The aim of this chapter was to investigate the change to the GR caused by those aberrant sacral reflexes that emerge with spinal cord injury by looking at the modulation of the sacral somatic pudendo-anal reflex (PAR), as a surrogate for the pudendo-urethral reflex (PUR), with autonomic bladder function, for assessing residual supra-sacral bladder and sphincter function and development of aberrant reflexes in SCI subjects.

3.2 Methods

3.2.1 Project Approval

Ethics approval was sought and approved at Institute of Orthopaedics and The Royal National Orthopaedics Hospital Trust from The Joint Research and Ethical Committee.

3.2.2 Screening Patient Population for Suitability

Inclusion Criteria

Twenty-four patients between the ages of 18-65 were recruited at least twenty-four months post injury having neurologically chronic and stable lesions. They all had an upper motor neuron suprasacral T10 and above, incomplete or complete spinal cord injury. This was based on a study (Wyndaele, 1997) confirming that lesions of the vertebrae above T10 give a hyperreflexic activity in the LUT and those below L2 provoke areflexia. Complete and incomplete patients with SCI were included with either demonstrable NDO and or DSD as indicated by previous urodynamic investigation reports or who were being prescribed bladder suppressant medication (anti-cholinergic medications including: oxybutynin, toltarodene or detrunorn). Neurogenic detrusor overactivity was defined, for the purposes of this study, as the presence of a detrusor pressure rise of at least >15cmH_2O on previous cystometric investigation.

Exclusion Criteria

Patients with SCI of less than twelve months were excluded to avoid the effects of acute SCI (spinal shock) on the lower urinary tract. No patients below the age of eighteen were included in the study. Patients with lesions at or below sacral level were excluded. Patients were also excluded if they had a history of any implanted device for bladder function or if they had a surgical procedure at any time to the bladder (e.g. clam) or bladder outlet, such as sphincterotomy or bladder neck incision, or wall stents, or

any major surgery for the bladder, such as an augmentation cystoplasty. Patients with botulinin toxin interventions to either the bladder or the bladder outlet were excluded. Any presence of cardiovascular conditions, current or historical, was also an exclusion factor, to allow the maximum margin of safety whilst performing cystometry to avoid the small risk of autonomic dysreflexia during cystometry.

3.2.3 Subjects Details

Subjects included 5 non-SCI volunteers, and the 14 incomplete SCI (iSCI-table 3.1) and 10 complete SCI (cSCI-table 3.2) subjects who met the inclusion criteria. All subjects who participated in this study signed a consent form having first been fully briefed and given the opportunity to have their questions answered. Urological management details were taken from the subject.

3.2.4 Neurological Examination- Performed By Attending Physician

Both non-SCI volunteers and spinal cord injured subjects gave fully informed consent to testing and anonymous publication of results. All SCI subjects were asked to cease taking anti-muscarinic medication at least four days prior to testing. Subjects underwent a full neurological examination, as per the 'Standard Neurological Classification of Spinal Cord Injury' protocol used in the Royal National Orthopaedic Hospital NHS Trust (adapted from the American Spinal Injury Association, figure 1.5). Motor function of 10 key muscles was assessed on each side of the body. These included the finger flexors at the distal phalanx of the middle (third) digit for level C8 and the abductor of the little (fifth) digit for level T1. A score ranging from 0 ± 5 was awarded for each muscle, with a score of 0 representing no detectable contraction and a score of 5 for normal muscle strength. An overall motor score out of a possible 100 (100 indicating normal motor function) was derived. Sensory function was assessed on

subject	ASIA grade	age of injury (years)	urological management	bladder suppressant
P01	B	7	spont void	+
P04	B	10	SPC	-
P05	B	4	CISC	+
P07	D	16	urge	On need
P08	B	17	CISC	+
P13	C	3	SPC	+
P14	C	2	indwelling	+
P16	D	4	urge	-
P18	B	3	CISC	+
P19	C	7	conveen	+
P20	D	11	CISC	-
P22	D	5	CISC on urge	+
P23	C	3	CISC on urge	-
P26	D	3	urge	-
mean±stdev		6.7 ± 4.9		

Table 3.1 Details Of Incomplete Spinal Injured Subjects

The iSCI subjects are tagged with the letter P followed by a numerical digit in the first column to preserve their anonymity- their label throughout the whole study.

Urological Management:
I '+' denotes a subject on bladder suppressant medication;
'-' denotes that subject was not on bladder suppressant;
'spont void' denotes that a subject voids spontaneously;
'SPC' denotes the subject has a suprapubic catheter;
'urge' indicates that the subject voids on urge;
'indwelling' indicates that the subject has an indwelling catheter;
'conveen' indicates that the subject wears a conveen/condom sheath;
'CISC' indicates the subject employs clean intermittent self-catheterization.

subject	age of injury (years)	urological management	bladder suppressant
P03	5	SPC	+
P06	4	SPC	+
P09	11	conveen	-
P10	17	CISC	+
P11	18	CISC	+
P12	9	SPC	+
P15	2	CISC	+
P17	27	conveen	-
P21	14	conveen+ CISC	-
P25	4	CISC	-
mean±stdev	11.1 ± 7.9		

Table 3.2 Details Of Complete Spinal Injured Subjects

The cSCI subjects are tagged with the letter P followed by a numerical digit in the first column to preserve their anonymity- their label throughout the whole study. They are all classified according to the ASIA/IMSOP Impairment Scale with grade A.

Urological Management:
I '+' denotes a subject on bladder suppressant medication;
'-' denotes that subject was not on bladder suppressant;
'spont void' denotes that a subject voids spontaneously;
'SPC' denotes the subject has a suprapubic catheter;
'urge' indicates that the subject voids on urge;
'indwelling' indicates that the subject has an indwelling catheter;
'conveen' indicates that the subject wears a conveen/condom sheath;
'CISC' indicates the subject employs clean intermittent self-catheterization.

both sides of the body for light touch (principally testing posterior columns) and pin prick (principally testing spinothalamic pathways) sensation over the 28 dermatomes from C2 to S4/5. At each level a score of 2 was given for normal sensation, 1 for impaired sensation, and 0 for no sensation. As a result, a maximum score of 112 was available for each test. Neurological level of injury (NLI) was determined as the most caudal spinal segment with normal sensory and motor function. Each patient was also classified between neurologically complete and incomplete by determination of the presence of a voluntary anal contraction and 'deep anal sensation' according to the American Spinal Injury Association (ASIA) impairment grading; from grade A (neurologically complete) through to grade E (normal).

3.2.5 Cystometry Set-Up

By adhering to standard sterile urological procedures, the attending clinician or specialist urology nurse catheterised the subject with the filling line attached with a 3-way-tap to a 10 French catheter carrying a standard 4.5 French detrusor pressure catheter (figure 3.1). The filling line was connected to a pump (Lectromed, UK) with room temperature sterile saline as the infusion fluid. Medium fill cystometry was performed at 30-50ml/min with room temperature sterile saline. Blood pressure monitoring was not generally carried out during the cystometry, but signs or symptoms of autonomic dysreflexia were strictly monitored, especially in the patients who had cervical and higher thoracic lesions. The outlet of the bladder pressure line was connected via a 3-way tap to a pressure transducer, which was connected to a 10 ml syringe containing sterile water / NaCl used to flush the pressure line. Prior to insertion of the pressure line, the transducer was zeroed to air and connected to the software data acquisition system so that intravesical pressure, which was consistent with detrusor activity, was recorded to predict the onset of neurogenic detrusor

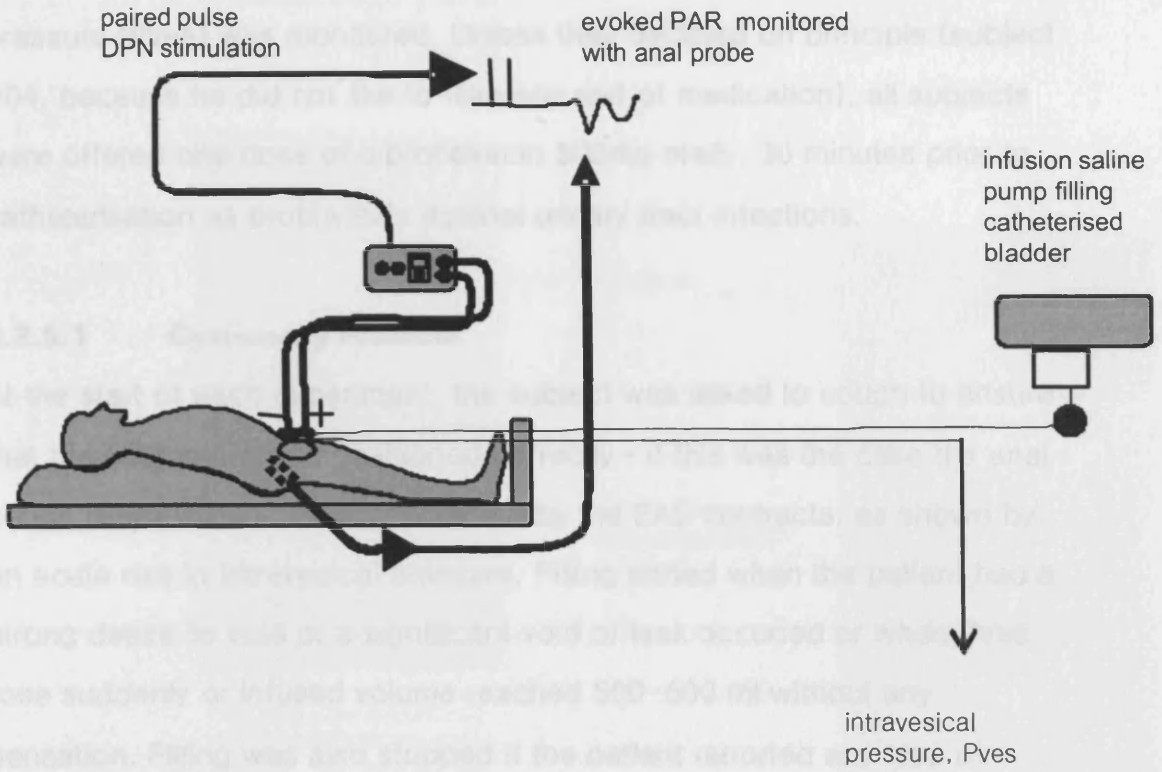


Figure 3.1 Set up for modulation of the bladder guarding response during filling study

The experimental arrangement of the subject is shown with the dorsal penile nerve stimulation (DPN) with its evoked responses, the pudendo-anal reflex (PAR). The catheterised subject connected up to the infusion saline pump via a filling line, with a pressure line and anal probe monitoring the intravesical pressure and pudendo-anal reflex response respectively.

overactivity in spinal injured subjects. The bladder was filled retrogradely with a filling line using sterile saline at room temperature and intravesical pressure (Pves) was monitored. Unless they declined on principle (subject P04, because he did not like to take any sort of medication), all subjects were offered one dose of ciprofloxacin 500mg orally, 30 minutes prior to catheterisation as prophylaxis against urinary tract infections.

3.2.5.1 Cystometry Protocol

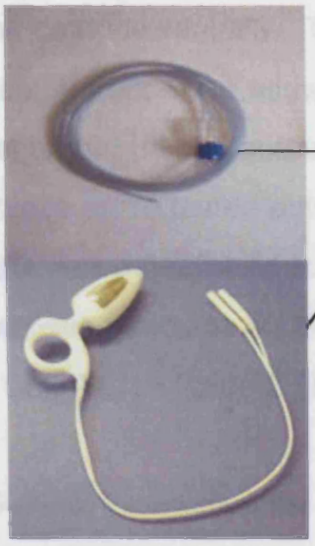
At the start of each experiment, the subject was asked to cough to ensure that the equipment was positioned correctly – if this was the case the anal cough reflex would be elicited– whereby the EAS contracts, as shown by an acute rise in intravesical pressure. Filling ended when the patient had a strong desire to void or a significant void or leak occurred or when Pves rose suddenly or infused volume reached 500–600 ml without any sensation. Filling was also stopped if the patient reported any type of discomfort or asked for the study to not continue.

3.2.6 External Anal Sphincter Electromyogram (EAS EMG) Set-Up

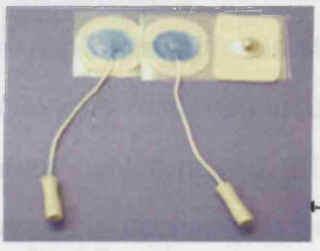
An anal probe (figure 3.2) incorporating longitudinal (Binnie *et al.* 1997) electrodes was inserted into the anus of the subject using a generous amount of KY-gel. It was connected to the amplifier and computer software data acquisition system to give a read-out of the electromyographic activity of the EAS muscle. The data acquisition system was set to allow a band pass of 20 Hz to 10 kHz with a sweep-time of 200 msec. EMG signals were filtered (73 dB below 300 Hz and above 2 kHz) and amplified before being sampled (4 kHz) by a computer for analysis (CED, Cambridge Electronic Design 1401*plus* SPIKE 2) and storage.

monitoring

A standard detrusor pressure catheter (4.5 French, EMS Medical Grou LTD, Clos., UK and Mediplus, Bucks) was used to monitor intravesical pressure.



The anal probe (ANUFORM, NEENHealthCare,Lancashire) monitors the pudendo-anal reflex, PAR of the external anal sphincter, EAS. The probes insertion was aided with KY gel.



stimulation

Two self-adhesive silver-silver chloride electrodes were used for DPN electrical stimulation.

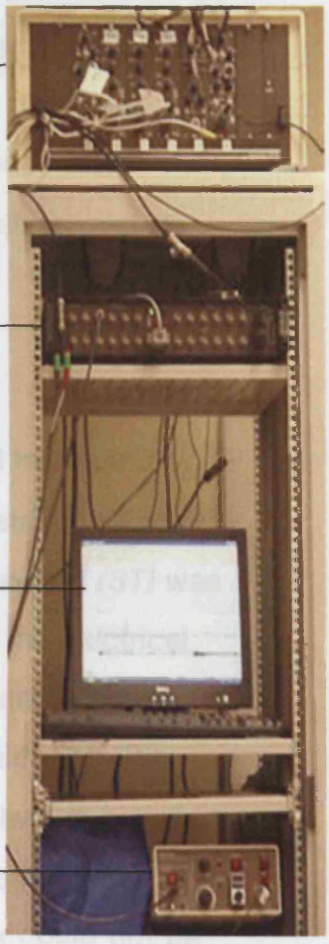
The earth electrode shown on the far right was placed on the bony part of the hip bone after the skin was cleaned with an alcohol swab. It was used to reduce the noise to signal ratio in the EAS EMG monitoring with the Anuform anal probe.

amplifier

CED 1401 *plus* data acquisition system

Spike 2 software computer-data display

digitimer



The electrically isolated constant current stimulator :Digitimer, allowed variation of DPN stimulus strength and timing. (model DS7, Welwyn Garden City, Hertfordshire, UK).

Figure 3.2 The Laboratory Equipment Set-Up

3.2.7 Dorsal Penile Nerve Stimulation Set-Up

The dorsum of the proximal shaft of the penis was shaved and cleaned with alcohol swabs. Two cutaneous self-adhesive silver-sliver chloride electrodes were placed in a dorso-ventral orientation, with the anode dorsally and the cathode ventrally. The electrodes were connected to an isolated constant current nerve stimulator (Digitimer, UK, figure 3.2) with a pulse-width set to 200 μs and output to x10, which supplied stimulation at variable amplitudes as 10 paired pulses at a repetition rate of 0.2 Hz. The stimulus strength was established such that the PAR response was recorded on real-time tracings on the software data acquisition system (SPIKE 2 plus CED 1401- figure 3.2).

3.2.7.1 General Parameters for DPN Stimulation

The stimulus strength on the Digitimer was set to 1mA and increased by 1-5mA increments manually. With both neurologically intact subjects (non-SCI) and those with incomplete lesions (iSCI), *sensory threshold (ST)* was determined as the stimulation at which the subject sensed the electrical stimulation. The minimum stimulus strength required to reliably elicit an external anal sphincter response visually, as seen as an anal wink (the cutaneoanal reflex - which has its afferent and efferent pathways in the pudendal nerve and is abolished if S4 is transected), or the average pudendo-anal reflex (PAR) response trace (if the anal wink could not be detected) from 10 paired electrical pulses of DPN was defined as the *reflex threshold* for the pudendo-anal reflex (PAR). *Working threshold (WT)* of DPN electrical stimulation, for the purposes of the rest of the study was set at a stimulus strength of at least twice that of the reflex threshold for the PAR response in complete SCI (cSCI) subjects, and as close to this as was possible (tolerable) in incomplete and intact subjects. This doubling of the reflex threshold has been shown previously to reliably suppress

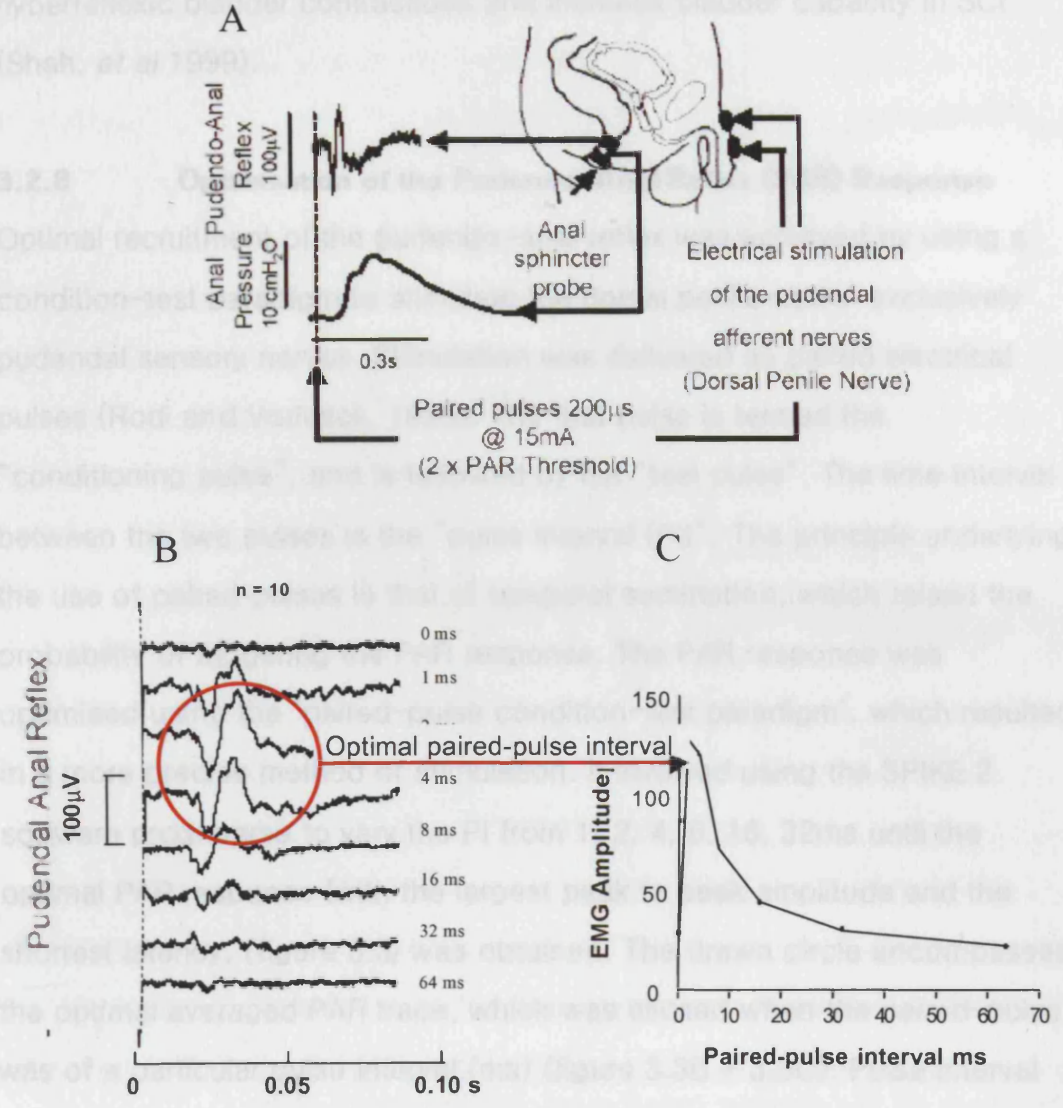


Figure 3.3 The Normal Pudendo-Anal Reflex (PAR) And The Condition Test Paired Pulse Paradigm In Operation

D. By selective pudendal afferent nerve stimulation of the dorsal penile (or dorsal clitoral) nerves the PAR (as a surrogate of the PUR) reflex is evoked manifesting as a short-lived contraction of the EAS (EUS) recorded using an anal plug electrode and a longer anal pressure rise.

E. Pudendal anal reflex response traces shown for this non-SCI subject for a range of pulse intervals for the paired-pulse stimulation. The 'red circle' indicating (in graph C) that at a 14ms pulse interval an optimal compound motor evoked potential response was elicited from the anal sphincter.

hyperreflexic bladder contractions and increase bladder capacity in SCI (Shah, *et al* 1999).

3.2.8 Optimisation of the Pudendo -Anal Reflex (PAR) Response

Optimal recruitment of the pudendo-anal reflex was achieved by using a condition-test paradigm to stimulate the dorsal penile nerve: exclusively pudendal sensory nerves. Stimulation was delivered as paired electrical pulses (Rodi and Vodusek, 1995). The first pulse is termed the "conditioning pulse", and is followed by the "test pulse". The time interval between the two pulses is the "pulse interval (PI)". The principle underlying the use of paired pulses is that of temporal summation, which raised the probability of triggering the PAR response. The PAR response was optimised using the 'paired-pulse condition-test paradigm', which resulted in a more precise method of stimulation. It involved using the SPIKE 2 software programme to vary the PI from 1, 2, 4, 8, 16, 32ms until the optimal PAR response (with the largest peak to peak amplitude and the shortest latency, (figure 3.3) was obtained. The drawn circle encompasses the optimal averaged PAR trace, which was elicited when the paired-pulse was of a particular pulse interval (ms) (figure 3.3B + 3.3C). Pulse interval PAR optimisation was most favourable when there was some fluid in the bladder- i.e. not with an empty bladder.

3.2.9 Criteria Of Analysis Of The Pudendo -Anal Reflex Response

Two parameters of the PAR response were taken into consideration during analysis: the peak to peak amplitude; and the latency of the response, which gave a measure of the time period between the test pulse and the onset of the PAR response. In all cases the peak to peak amplitude of the PAR response was standardised to the PAR peak to peak amplitude of the PAR response of the empty bladder in both bi/tri-phasic PAR (figure 3.4A) and polyphasic PAR (figure 3.4B). These differing waveforms are known to

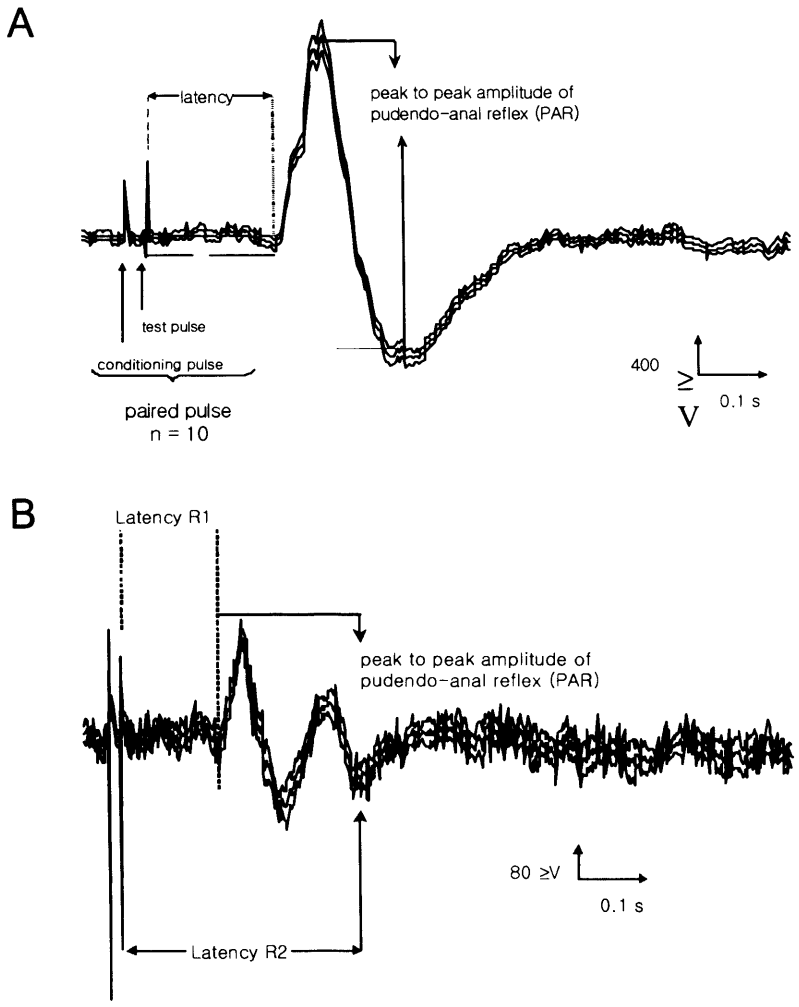


Figure 3.4 Waveforms Of The Averaged Normal Pudendo-Anal Reflex (PAR)

Differences in waveforms of the evoked response are thought to be due to the relation between the recording electrode and the muscle in question. Also the muscle may contract differently in different subjects.

A Example Of Bi/Tri-Phasic PAR
The PAR was elicited from 10 paired electrical pulses using dorsal penile nerve stimulation (mean ± sem) showing parameters measure. The paired pulse consists of the conditioning pulse followed by the test pulse (Rodi and Vodusek, 1995). The latency of the response is generally measured from the test pulse stimulation and ranges from 25-35 ms (Dyro and Yalla, 1986) and is expressed in milliseconds, ms. The peak to peak amplitude of the PAR response indicates the level of EAS (surrogate for EUS) activity and is expressed in microvolts, ≥V, and then normalised to the peak to peak amplitude of the PAR response of the empty bladder of the subject.

B Example Of Polyphasic PAR
The averaged pudendo-anal reflex elicited from 10 paired electrical pulses using dorsal penile nerve stimulation (mean ± sem) [as seen in subject P15]

occur only as a result of the relationship between the recording electrode and the muscle in question which may contract differently in different individuals.

3.2.10 Experimental Protocol

The bladder was drained of urine at the start of each bladder fill. A PAR was elicited and termed 'the optimised PAR of an empty bladder' denoted by PARempty or PAR0ml. In some subjects a control fill was done, following closely the intravesical pressure, Pves, to assess at what volume in the bladder fill the PAR should be elicited for end fill volume, PARefv. In other subjects the PAR was elicited throughout the bladder fill at 50 to100 ml intervals so including the PARefv. In all experiments, the analysis parameters elicited were the PARempty, PARefv. The parameter PARefv was elicited in non-spinal subjects when strong urge and desire to void was experienced; in SCI subjects this value was taken at the volume just prior to an uninhibited contraction- as predicted by a rise of >15cmH_20 in Pves, which was monitored closely throughout as a predictive indicator of an NDO contraction.

3.2.11 Repeatability Testing the of PAR-monitoring

As it was not always possible for a subject to participate in a study more than once, to test the repeatability of PAR analysis, when time constraints permitted, several bladder fill runs were aimed for. To allow this, rate of fill was increased from 20 ml/min to 30-50 ml/min. Only in some cases did subjects return to participate on a separate study day.

3.2.12 Measurement Of Bladder Capacity

In all cases, bladder filling was stopped when there was a leak of urine also termed 'firing off' or a sustained (>10sec) rise in intravesical pressure of >15cmH_20. The residual volume of urine in the bladder (RV) was

manually aspirated out and measured. The volume of urine fired off or leaked (VL) during a period of NDO was collected and measured. Bladder end fill volume (EFV) or bladder capacity (BC) was calculated thus: RV + VL = BC. In non-SCI subjects the bladder capacity was the total amount voided voluntarily.

3.2.13 Statistical Analysis

Data was analysed using the Spike program. All information was treated confidentially and conformed to the regulations described in the Data Protection Act. All PAR values underwent a process of standardisation or normalisation. This term refers to all PAR values elicited in one subject being ratioed (divided by) to the PAR of the empty bladder (such that the normalised PAR value for the empty bladder in each subject was always equal to 1). All data was pooled and expressed as a mean ± SD. Clinical statistical significance between SCI and non-SCI subject data was determined with 95% confidence interval using an unpaired 2-tailed t-test with Welch's correction. [The unpaired t test assumes that the two populations have the same variances. Since the variance equals the standard deviation squared, this means that the populations have the same standard deviation). A modification of the t test (developed by Welch) is used when one is unwilling to make that assumption]. Repeatability was assessed using intra subject correlations (also known in the statistical literature as intra-class correlations, (ICCs)). The ICC is the ratio of between subject variance to (between subject variance plus within subject variance). A higher ICC (closer to 1) value was associated with better repeatability of the parameter in question.

3.3 Results

3.3.1 Subjects Details

Non-spinal injured subjects

Five non-SCI subjects were used in this study with an average (mean±stdev) age of 35.4 ± 14.4 years and an average bladder end fill volume of 656 ± 62.6 mL. These subjects were all graded with ASIA E signifying normal motor and sensory function with a maximum motor score of 100 (all key muscles scored a maximum of 5 with active movement against full resistance [normal]) and a maximum score of 112 for both light touch and pin prick assessment (all key sensory points scored a maximum of 2 [normal]).

Incomplete SCI subjects

Details of the 14 incomplete SCI participants are summarised in table 3.3. In table 3.3 there were 6 thoracic and 8 cervical incomplete SCI subjects classified as 5 ASIA B, 4 ASIA C and 5 ASIA D, of whom 8 were on bladder suppressants and 5 were not. The average (mean±stdev) age of the injury was 6.7 ± 4.9 years, mean motor score was 55 ± 24 and mean light touch score and pin prick score were 82 ± 14 and 84 ± 17 respectively.

Complete SCI subjects

Of the complete ten SCI subjects shown in table 3.4, there were 8 with thoracic SCI and 2 with cervical breaks with 6 on bladder suppressants and 4 not taking any bladder medication. The average (mean±stdev) age of the injury was 11.1 ± 7.9 years, mean motor score was 37 ± 17 and mean light touch score and pin prick score were 46 ± 18 and 45 ± 17 respectively.

subject	NLI (motor/sensory)	ASIA	motor score	light touch score	pin prick score
P01	T1/T9	B	94	84	79
P04	C5/T7	B	29	66	60
P05	T1/T9	B	50	74	64
P07	normal/T2	D	92	112	108
P08	T1/T10	B	54	68	91
P13	C5/T7	C	61	92	83
P14	T1/T9	C	20	72	73
P16	C5/C6	D	31	60	74
P18	C8/C7	B	39	68	70
P19	C7/C8	C	36	70	70
P20	T1/T9	D	72	88	88
P22	C5/T3	D	31	92	92
P23	C6/T4	C	55	82	112
P26	C4/C3	D	89	101	106
mean ± stdev			55 ± 24	82 ±14	84 ± 17

Table 3.3 **ASIA/IMSOP Impairment Scale Results For Incomplete Spinal Injured Subjects- Performed By The Attending Clinician**

The spinal lesion level is shown by the neurological lesion injury, NLI, with the most caudal normal motor level indicated first, followed by the most caudal normal sensory level. These iSCI subjects were graded ASIA B, C and D:

B sensory but not motor function is preserved below the NLI and includes the sacral segments S4-S5.

C motor function is preserved below the NLI and more than half of the key muscles below the NLI have a muscle grade less than 3.

D motor function is preserved below the NLI, and at least half of the key muscles below the NLI have a muscle grade of 3 or more.

Out of a possible 100 (normal function) the motor score resulted from assessing 10 key muscles either side of the body from 0 ± 5 each.
Out of a possible 112 sensory function was assessed on both sides of the body for light touch (principally testing posterior columns) and pin prick (principally testing spinothalamic pathways) sensation over the 28 dermatomes from C2 to S4/5, scored 2 for normal sensation, 1 for impaired sensation, and 0 for no sensation.

subject	NLI (motor/sensory)	motor score	light touch score	pin prick score
P03	T1/T8	+25	60	60
P06	None/C4	0	12	12
P09	T1/T7	50	70	58
P10	T1/T6	46	59	57
P11	T1/T5	20	48	48
P12	T1/T5	50	54	54
P15	T1/T6	50	54	54
P17	T1/T5	50	46	46
P21	C5/C4	34	16	16
P25	T1/T4	50	45	45
mean±stdev		37 ± 17	46 ±18	45 ± 17

Table 3.4 **ASIA/IMSOP Impairment Scale Results For Complete Spinal Injured Subjects- Performed By The Attending Clinician**

The spinal lesion level is shown by the neurological lesion injury, NLI, with the most caudal normal motor level indicated first, followed by the most caudal normal sensory level. These cSCI subjects were graded ASIA A:

A no sensory or motor function preserved in the sacral segment S4-S5

Out of a possible 100 (normal function) the motor score resulted from assessing 10 key muscles either side of the body from 0 ± 5 each.

Out of a possible 112 sensory function was assessed on both sides of the body for light touch (principally testing posterior columns) and pin prick (principally testing spinothalamic pathways) sensation over the 28 dermatomes from C2 to S4/5, scored 2 for normal sensation, 1 for impaired sensation, and 0 for no sensation.

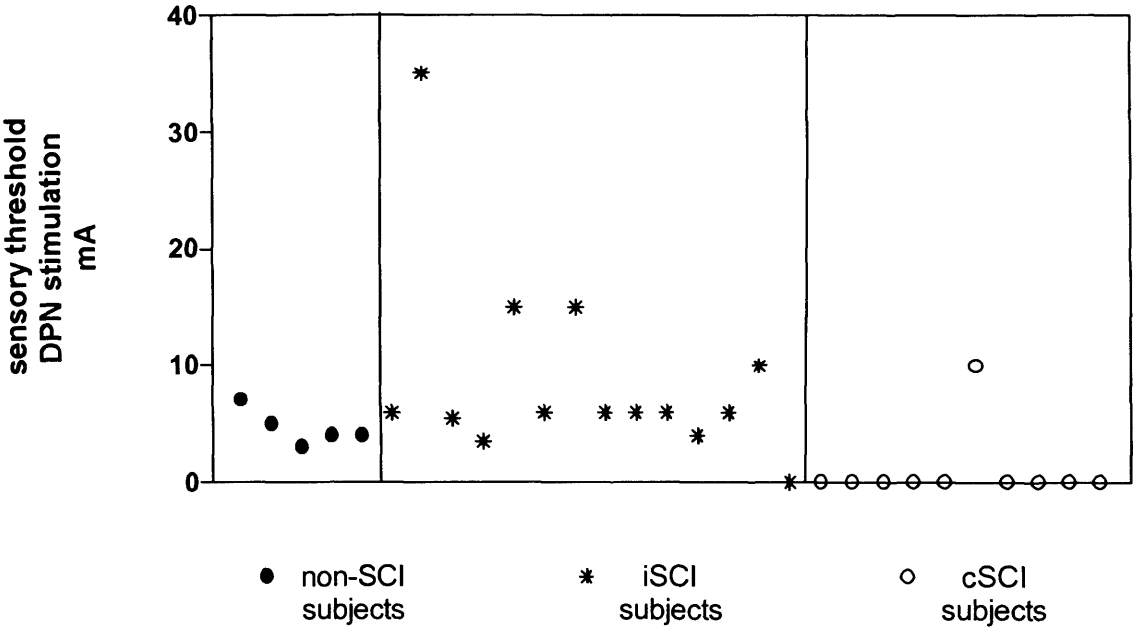
3.3.2 General Parameters of DPN Stimulation

Sensory Threshold (ST)

The sensory threshold was defined as the DPN stimulation where the subject could initially feel the electrical stimulation on the dorsal penile nerve, and has been plotted for all subjects in figure 3.5. The table in figure 3.5 shows the mean sensory threshold for the 3 groups of subjects. The average (mean ± SD) ST for the non-SCI was 2.4 ± 0.8 mA showing that these neurologically intact subjects were very sensitive to electrical DPN stimulation. The average ST for the iSCI subjects, 9.5 ± 2.3 mA, was greater than that for the non-SCI subjects, due to varying degrees of impairment. Out of the iSCI subjects P14 (NLI T1 motor/T9 sensory; pin prick score of 73 and light touch score of 72) ASIA C had no sensory threshold- the reason for this remains unexplained. All but one of the cSCI subjects had no sensory threshold because of their lack of sensation at the level of DPN stimulation. An unexplained anomaly to this was P17 who had a sensory threshold of 10mA. According to his ASIA assessment his NLI was T1 motor, T5 sensory (zpp T5 sensory) and both pin prick and light touch scores of 46/112. The Spearman correlation coefficient, rs = -0.58 (confidence interval -0.78 to -0.27) indicated there to be a highly significant (p = 0.0008) negative relationship between the degree of neurological impairment and the sensory DPN stimulation threshold.

Reflex threshold

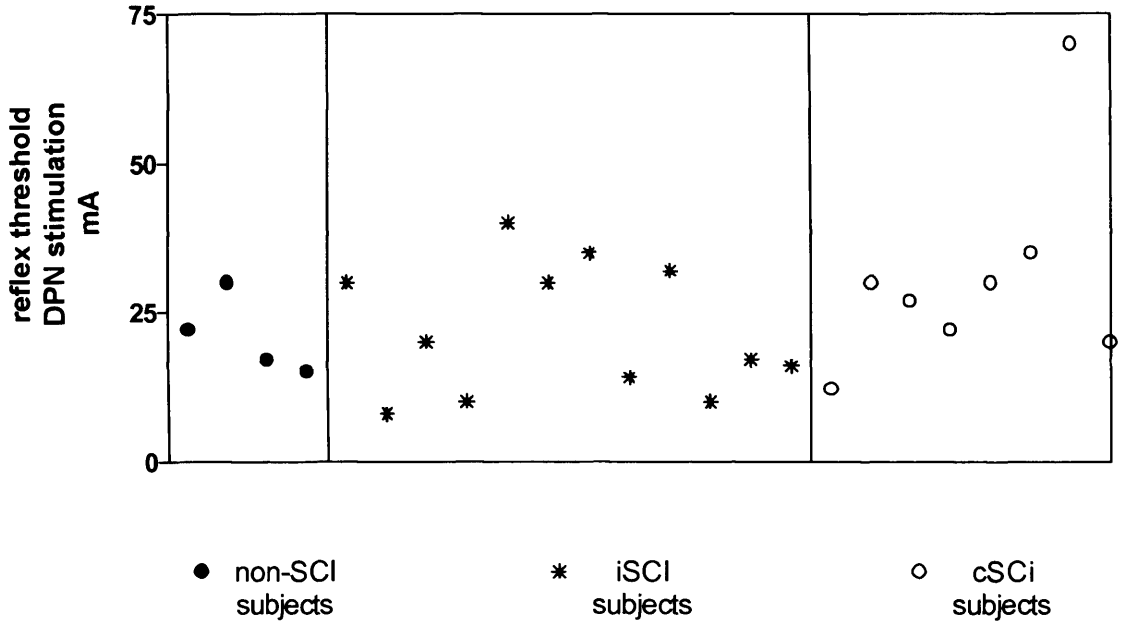
The reflex threshold stimulation was defined as the DPN stimulation needed to elicit the pudendo-anal reflex response in the external anal sphincter as monitored with the anal probe, sometimes seen as the 'anal wink' (figure 3.6), which is a short duration contraction of the external anal sphincter. The table in figure 3.6 shows the average (mean±SD) reflex



cohorts		ST mA mean ± SD
n=5	non-SCI	2.4 ± 0.8
n=13	iSCI	9.5 ± 2.3
n=9	cSCI	no sensation
n=1	cSCI	10

Figure 3.5 Sensory Threshold Parameter Established In All Subjects

Graph showing the sensory threshold (ST) in the 3 cohorts of subjects subjected to dorsal penile nerve stimulation (DPN). Spearman coefficient, rs= -0.58 indicates a negative relationship between sensory threshold and neurological impairment which was very significant: p = 0.0008 (confidence intervals -0.78 to -0.27).



cohorts	reflex threshold mA mean±SD
non-SCI	21.0 ± 3.3
iSCI	21.8 ± 3.1
cSCI	27.6 ± 5.2

Figure 3.6 Reflex Threshold Parameter Established In All Subjects

Graph showing the reflex threshold of the pudendo-anal reflex in the 3 cohorts of subjects subjected to dorsal penile nerve stimulation (DPN). Spearman coefficient rs= 0.07 (confidence intervals -0.3 to 0.4) showed a positive relationship between the reflex threshold and the neurological status of the subject which was not significant: p=0.7

threshold found in non-SCI was 21.0 ± 3.3 mA and found to be very comparable to that for the iSCI subjects 21.8 ± 3.1 mA. However the average reflex threshold in cSCI was greater at 27.6 ± 5.2 mA. Statistical analysis showed that although the reflex threshold that elicited a PAR response or anal wink had a positive relationship (Spearman coefficient rs= 0.07 (confidence intervals -0.3 to 0.4)) with the degree of neurological impairment of the subjects, this relationship was not significant (p=0.7).

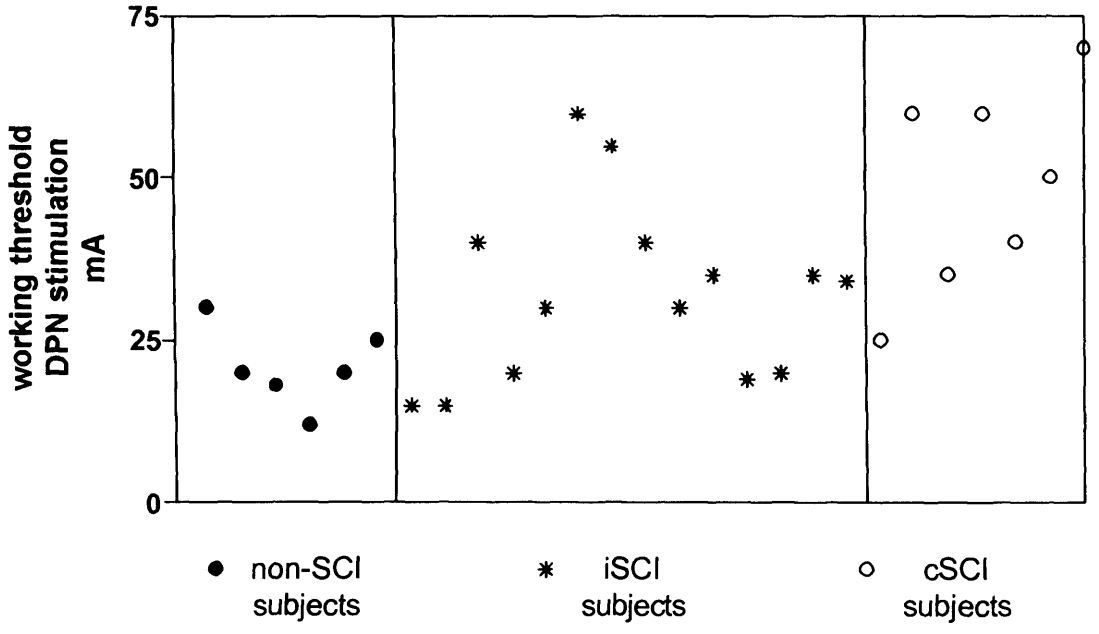
Working Threshold (WT)

The working threshold as defined as the DPN stimulation used throughout the experiment which elicited an optimal PAR response (where tolerable to the subject this was twice the motor threshold) - shown in figure 3.7. The average WT (mean±SD) for non-SCI subjects was 20.8 ± 2.5 mA and was greater in the iSCI subjects at 32.0 ± 3.7 mA and much greater in cSCI subjects at 45.0 ± 4.5 mA, due to their greater tolerability to electrical stimulation. Analysis indicated that WT had a positive relationship (Spearman correlation coefficient rs= 0.6 (confidence intervals 0.3 to 0.7)) with neurological impairment which was highly statistically significant p=0.0004 (figure 3.7).

3.3.3 Pudendo -Anal Reflex Response Optimisation

Optimal Pulse Interval (PI)

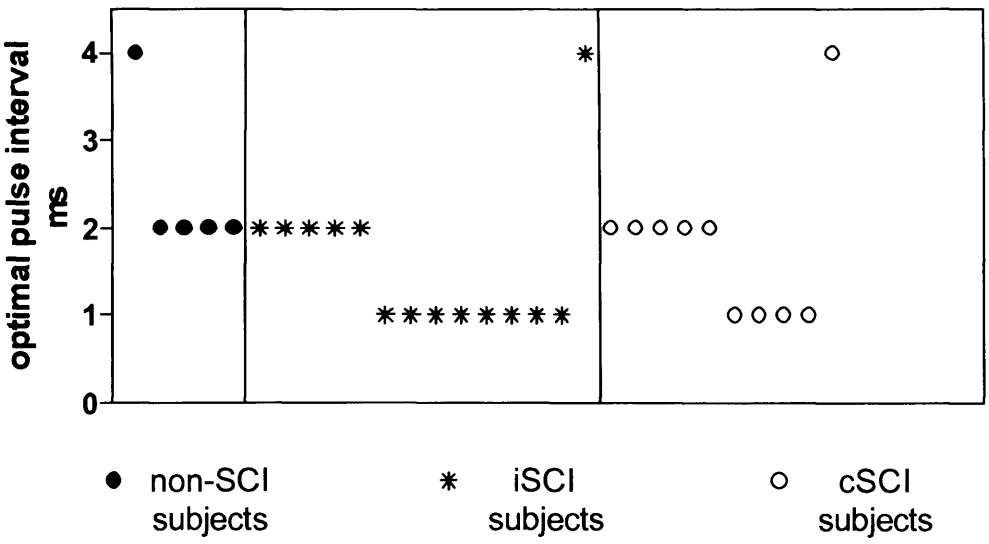
Optimal PI for the non-SCI subjects were found to be either 2ms (n=4) or 4ms (n=1), the average optimal PI being 2.5±0.8 ms (mean±SD, table in figure 3.8). Although a PI of 1ms only occurred in SCI subjects, the optimal PI for both iSCI (1.5±0.8 ms) and cSCI (1.8±0.9 ms) subjects was on average less than that for the non-SCI subjects, but not significantly so. For all subjects the overall optimal PI range was 1-2 ms, with 3 outliers at



cohorts	WT mA	
	mean ± SD	
non-SCI	20.8 ± 2.5	
iSCI	32.0 ± 3.7	
cSCI	45.0 ± 4.5	p = 0.0004

Figure 3.7 Working Threshold Parameter Established In All Subjects

Graph showing the working threshold (WT) in the 3 cohorts of subjects subjected to dorsal penile nerve stimulation (DPN). The WT was twice that of the reflex threshold where tolerable in the non-SCI and iSCI, although this was not always possible. Spearman correlation coefficient rs= 0.6 (confidence intervals 0.3 to 0.7) indicated a statistically significant (p = 0.0004) positive relationship between WT and neurological status, indicating that the WT increased with increasing neurological impairment.



	mean±stdev
● non-SCI subjects	2.5±0.8
✱ iSCI subjects	1.5 ±0.8
○ cSCI subjects	1.8 ±0.9

Figure 3.8 Pulse Intervals Eliciting Optimal PAR Responses

The graph shows the optimal pulse interval for the 3 groups of subjects with optimal pulse interval for each cohort in the table expressed as the mean±stdev. The values for these subjects were 1-2 ms, with 3 outliers at 4ms.

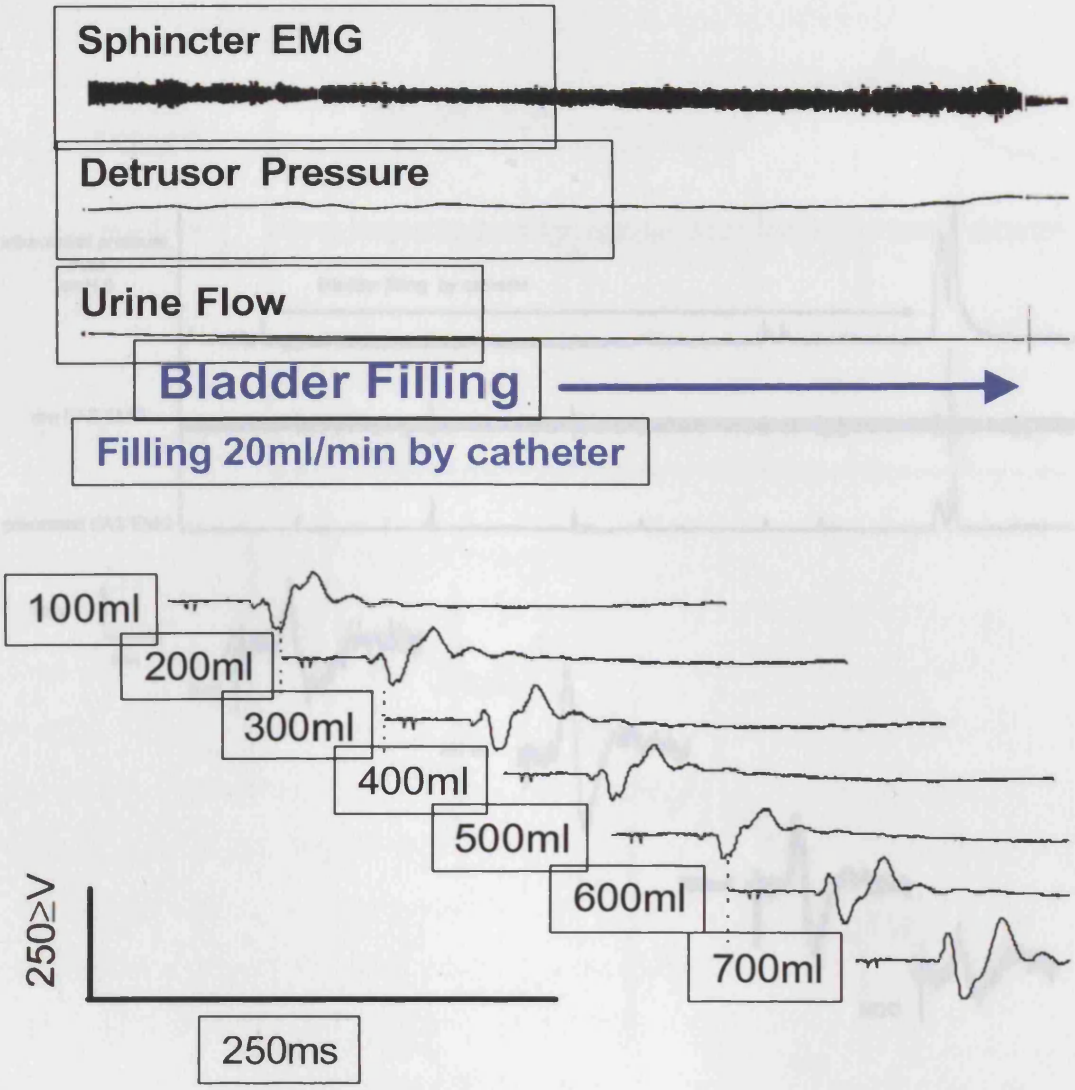


Figure 3.9 **Interaction Of The Somatic Pudendo-Anal Reflex Response With The Autonomic Effects Of Bladder Filling Cystometry In A Non-SCI Subject**

The top trace shows the sphincter EMG which built up as the bladder fills, with detrusor pressure remaining constant showing the high bladder compliance in this non-SCI subject. Sphincter EMG activity was analysed using the somatic PAR response evoked at each 100ml interval which increased in peak-to-peak amplitude as the bladder was filled.

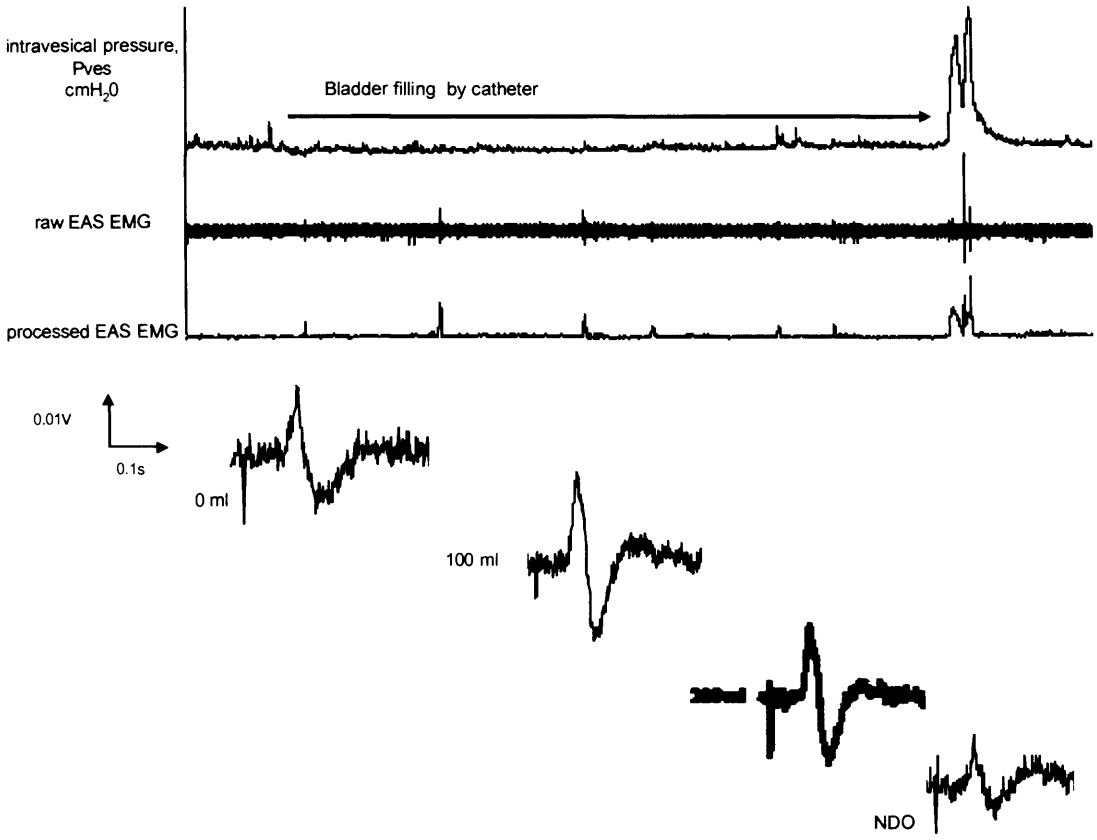


Figure 3.10 Interaction Of The Somatic Pudendal-Anal Reflex Response With The Autonomic Effects Of Bladder Function In An Incomplete SCI Subject (P08)

The 2 lower traces shows the external anal sphincter EMG, for which the build up as the bladder fills is seen more clearly by the 2 large spikes in the processed EMG, with intravesical pressure remaining constant showing the high bladder compliance in this iSCI subject. Sphincter EMG activity was analysed using the somatic PAR response evoked at each 100ml interval as the bladder was filled. PAR activity was attenuated during NDO in this subject.

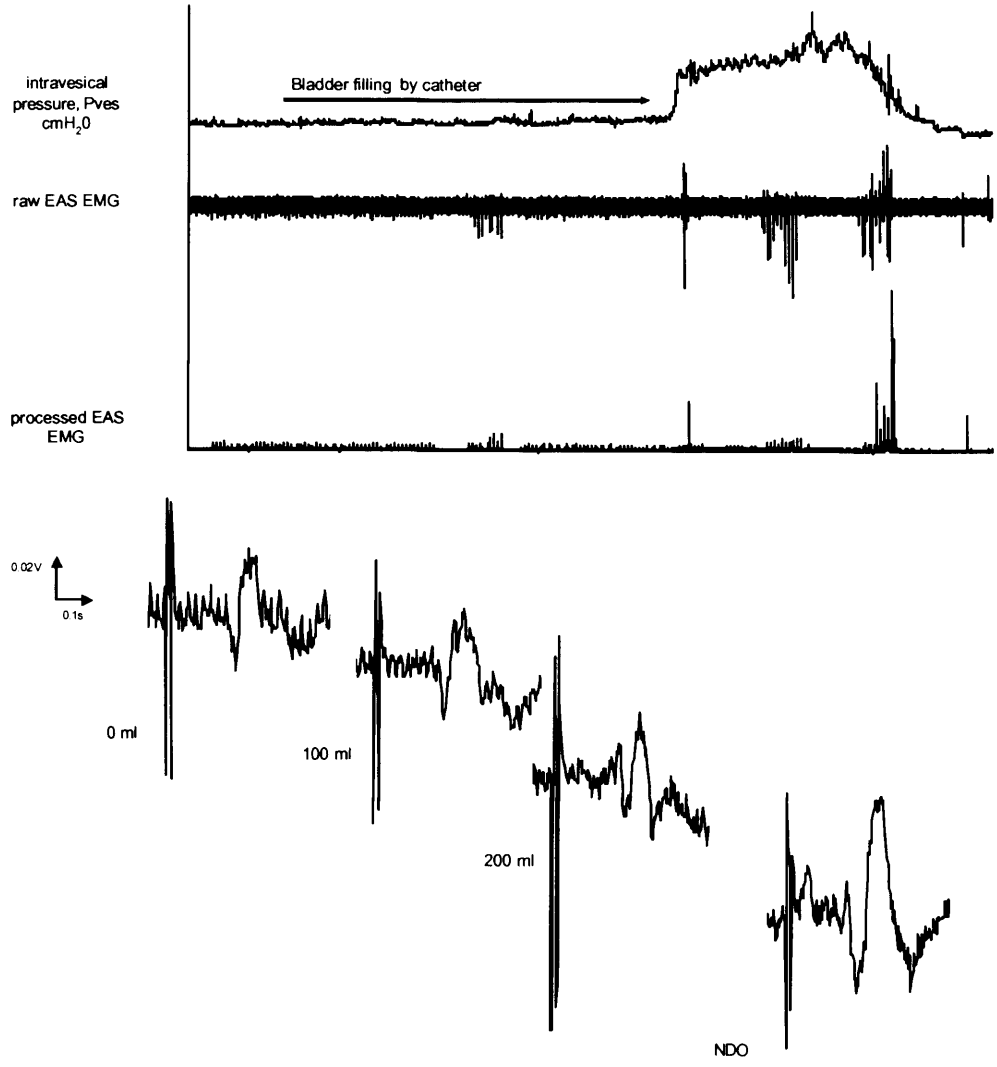


Figure 3.11 Interaction Of The Somatic Pudendal-Anal Reflex Response With The Autonomic Effects Of Bladder Function In A Complete Sci Subject (P10)

The 2 lower traces shows the external anal sphincter EMG as the bladder fills, with intravesical pressure remaining constant showing the high bladder compliance in this cSCI subject. Sphincter EMG activity was analysed using the somatic PAR response evoked at each 100ml interval as the bladder was filled. PAR activity was attenuated during NDO in this subject.

4ms. The average optimal PI was 1.79±0.9 ms, the greatest variability of optimal PI was seen in the incomplete spinal cord injured subjects. No significant correlation associating either level or extent of injury with the pulse interval parameter was seen.

3.3.4 Modulation Of The Guarding Response With Filling Cystometry

A typical example of the modulation of the PAR response with bladder filling in a non-SCI subject is shown in figure 3.9. Similar examples for an iSCI subject and a cSCI subject are shown in figures 3.10 and 3.11.

Latency of the pudendo -anal reflex response

During filling cystometry in the non-SCI subjects (figure 3.9) the sphincter EMG remained stable throughout bladder fill until the end fill volume was reached at which point the subject experienced a strong desire to void. PAR response was tested at this time in non-SCI subjects, and the latency analysed (figure 3.12). The normalised latencies of the PARefv responses for the SCI groups were also analysed. Figures 3.13 and 3.14 show normalised latencies of the PAR responses at end fill volume for the iSCI and the cSCI subjects' respectively. The mean normalised latencies between the two groups of SCI subjects (mean±SD: iSCI subjects 1.01 ± 0.06; cSCI subjects 1.02 ± 0.16) with non-SCI subjects (1.07 ± 0.09) were not significantly different (figure 3.15, iSCI subjects p = 0.58, cSCI subjects p = 0.26).

The Normalisation Procedure of the pudendo -anal reflex response

The normalisation PAR analysis technique that was employed in this study is shown in diagram 3.1. In summary the ratio was taken of the test condition, C_T to the baseline condition, C_0, a process resulting in the normalisation of the data. When $C_T = C_0$ the resulting value was equal 1. This was the value to which all test results were compared. The reason this

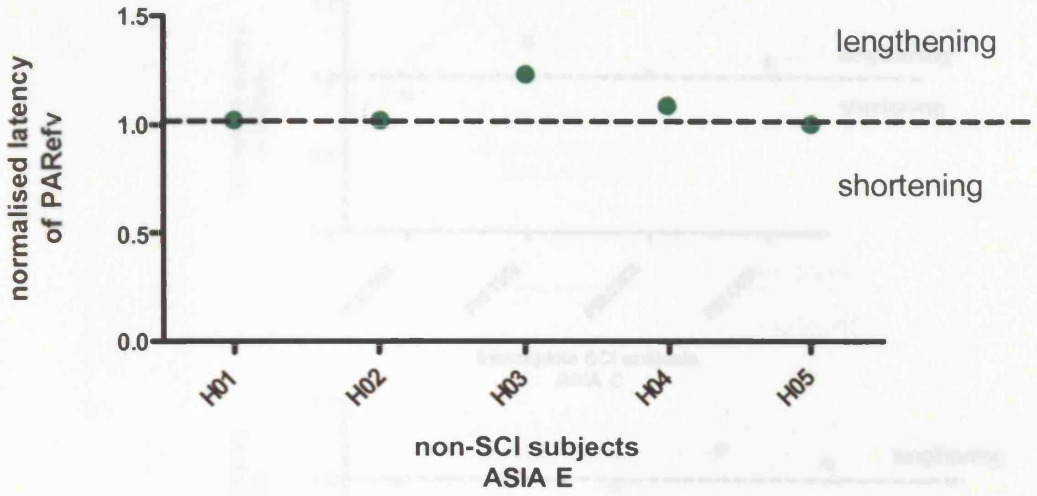


Figure 3.12 **Modulation Of The Normalised Latency Of The Pudendo-Anal Reflex Responses With Filling Cystometry In Non-SCI Subjects**

The graph shows the normalised latencies of the PAR responses tested at end fill volume representing the guarding responses in non-SCI subjects graded ASIA E and tagged H01 to H05 thereby preserving anonymity. The dashed line at y=1, indicates the normalisation procedure (diagram 3.1) such that any subject in whom end fill volume shortened the latency was above the dashed line, and any in whom the latency was lengthened was below the dashed line.

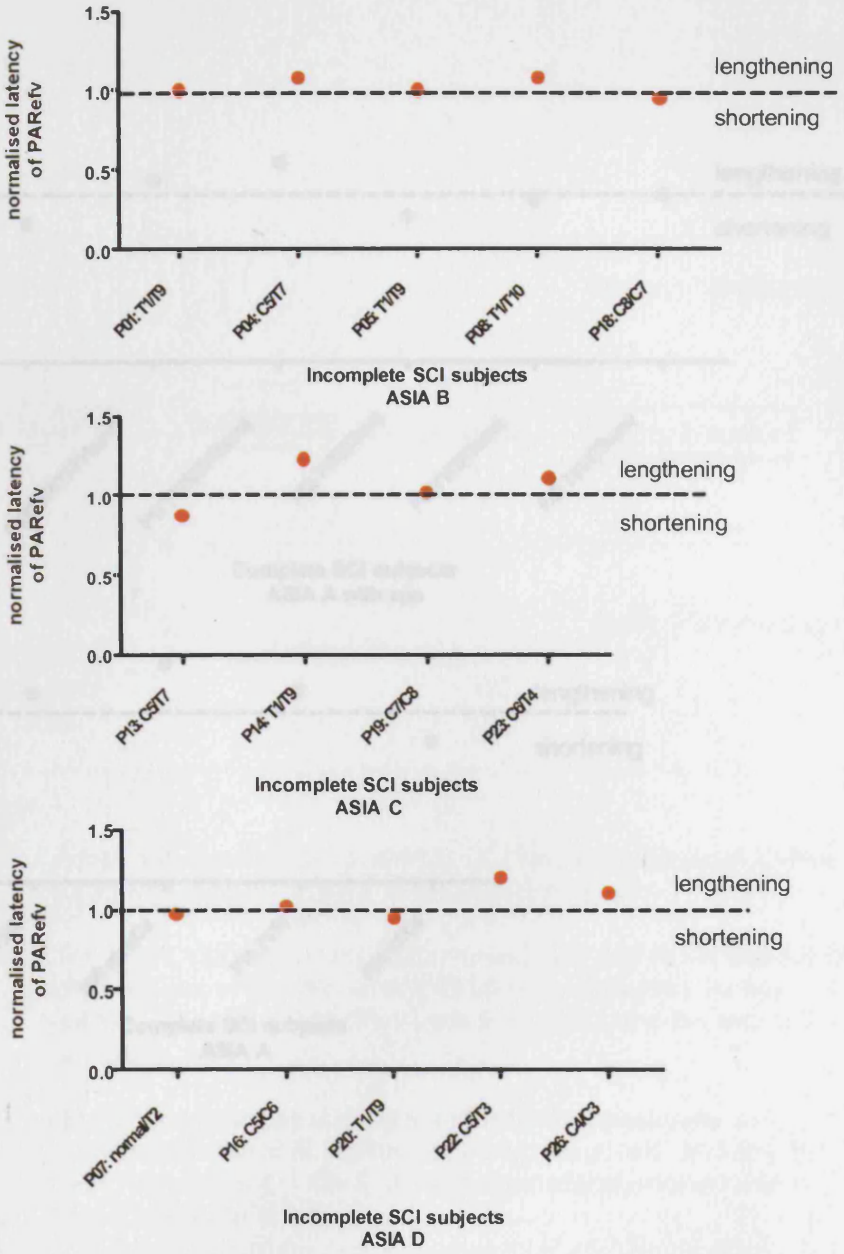


Figure 3.13 **Modulation Of The Normalised Latency Of The Pudendo-Anal Reflex Responses With Filling Cystometry In Incomplete SCI Subjects**

The graphs shows the normalised latencies of the PAR responses tested at end fill volume representing the guarding responses in iSCI subjects graded ASIA B, C and D and tagged with P followed by a numerical digit with their neurological level of injury (NLI: motor/sensory) thereby preserving anonymity. The dashed line at y=1, indicates the normalisation procedure (diagram 3.1) such that any subject in whom end fill volume shortened the latency was above the dashed line, and any in whom the latency was lengthened was below the dashed line.

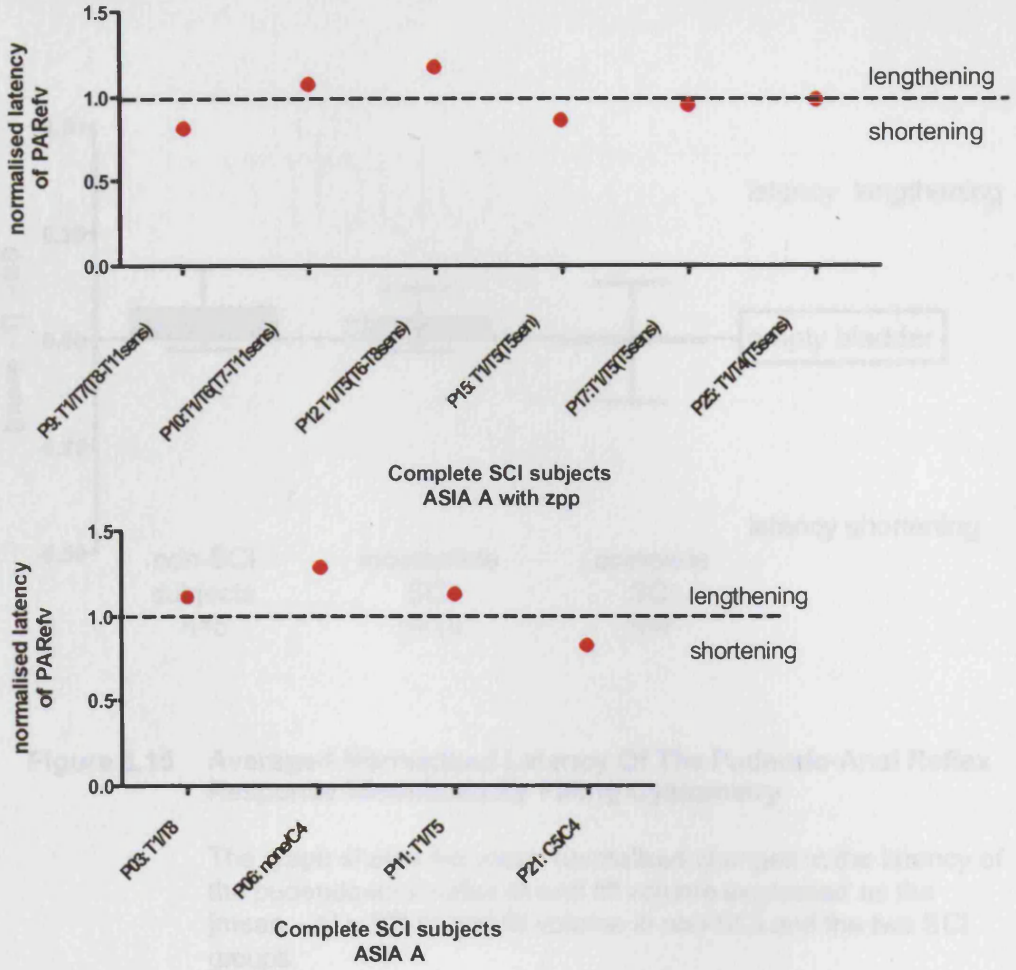


Figure 3.14 **Modulation Of The Normalised Latency Of The Pudendo-Anal Reflex Responses With Filling Cystometry In Complete SCI Subjects**

The graphs shows the normalised latencies of the PAR responses tested at end fill volume representing the guarding responses in cSCI subjects graded ASIA A and tagged with P followed by a numerical digit with their neurological level of injury (NLI: motor/sensory with zone of partial preservation, zpp, in the top graph, and those with no zpp in the lower graph) thereby preserving anonymity. The dashed line at y=1, indicates the normalisation procedure (diagram 3.1) such that any subject in whom end fill volume shortened the latency was above the dashed line, and any in whom the latency was lengthened was below the dashed line.

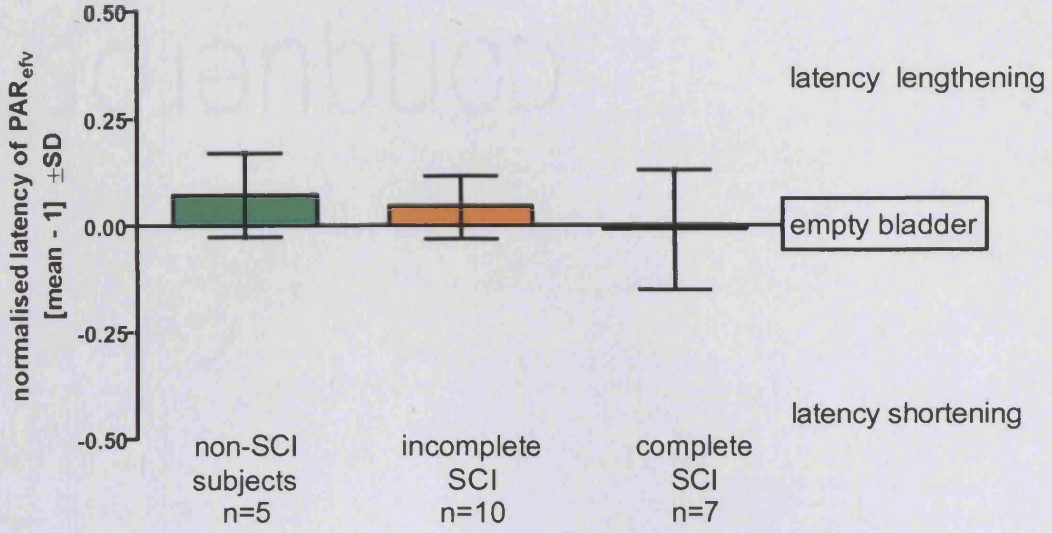


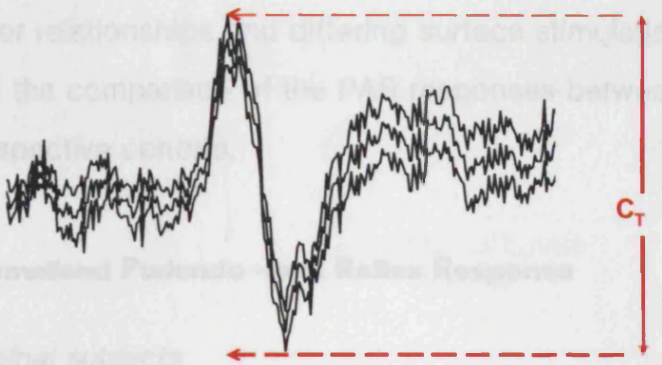
Figure 3.15 Averaged Normalised Latency Of The Pudendo-Anal Reflex Response Modulated By Filling Cystometry

The graph shows the mean normalised changes in the latency of the pudendo-anal reflex at end fill volume expressed as the [mean – 1] ο SD at end fill volume in non-SCI and the two SCI groups.

Groups in whom the latency of the PAR response was lengthened by end fill volume lay above the x-axis, and any in whom the latency of the PAR response was shortened was below the dashed line.

Although shorter latencies (below the x-axis) appeared to be associated with increased impairment, it was not significant when the normalised average latencies for the SCI groups were statistically compared to that of the non-SCI subjects (iSCI subjects: $p = 0.58$; cSCI subjects: $p = 0.26$).

where C_T is the peak to peak amplitude of test condition e.g. end fill volume; ; voiding; NDO; pelvic floor voluntary contraction



Normalisation Equatio

$$\frac{C_T}{C_0}$$

where C_0 is the peak to peak amplitude of the baseline condition: the empty bladder, or when the pelvic floor was relaxed (chapter 5)

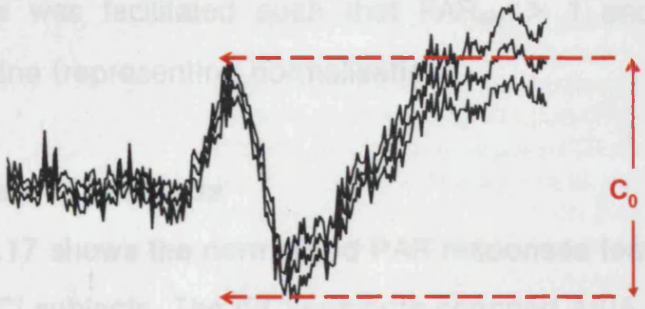


Diagram 3.1 Normalisation Technique Employed In The Analysis Of The Pudendo-Anal Response

This is an example of the normalisation technique shown using traces from a non-SCI subject. Both traces are averages from 10 paired pulses and shown as mean± SD.
The top trace indicates the type of trace from which baseline peak to peak amplitude was taken as denoted by C_0: it is the PAR elicited when the bladder was empty (chapters 3 and 4) or when the pelvic floor was relaxed (chapter 5 and 6). The bottom trace indicates the type of trace from which a condition peak to peak amplitude response was taken as denoted by C_T: it is the PAR elicited when the bladder was full during voiding, neurogenic detrusor overactivity or when the pelvic floor was contracted or when TMS was applied (chapter 5 and 6). The values for both C_0 and C_T were inserted into the equation for normalisation.

When $C_T = C_0$ the resulting value was = 1, it was to this that all test results were compared. I

normalisation technique was incorporated into the study was because in the raw data (appendix 1: latency; appendix 2: PAR; appendix 3: raw PAR waveform traces) big variations, between subjects, in the peak to peak amplitude were found. These variations were probably caused by the normal anatomical and physiological differences that are to be found in the normal population that resulted in differing recording electrode to the sphincter relationships and differing surface stimulation. Normalisation allowed the comparison of the PAR responses between the subjects and their respective cohorts.

The Normalised Pudendo -anal Reflex Response

Non-spinal subjects

Figure 3.16 shows that in the non-SCI subjects at end fill volume the PAR response was facilitated such that $PAR_{efv} > 1$ and data fell above the dashed line (representing normalisation).

Incomplete SCI subjects

Figure 3.17 shows the normalised PAR responses tested at end fill volume in the iSCI subjects. The iSCI subjects spanned ASIA grades B-D incorporating both cervical and thoracic injuries with a motor score of 55±24 (expressed as mean±SD) which was half that in the non-SCI subjects, and an average sensory score of 83±15 (approximately for both pin prick and light touch), which was 20% less than that in non-SCI subjects. All these functional modalities resulted in a bladder EFV of approximately half (394 ± 234 mL) that found in the non-SCI subjects.

Facilitation of the pudendo-anal reflex response with bladder filling cystometry in the incomplete SCI subjects

Normalised PARefv values greater than 1 indicated a preserved GR and the maintenance of continence. Seventy-one percent (10/14) of the iSCI

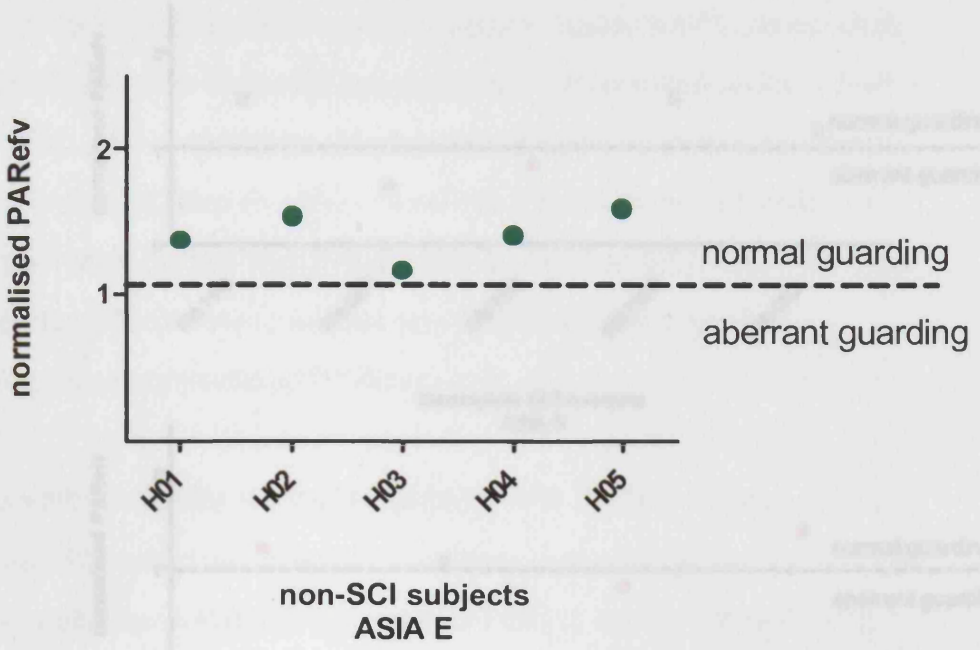


Figure 3.16 **Modulation Of The Normalised Pudendo-Anal Reflex Responses With Filling Cystometry In Non-SCI Subjects**

The graph shows the normalised PAR responses tested at end fill volume representing the guarding responses in non-SCI subjects graded ASIA E and tagged H01 to H05 thereby preserving anonymity. The dashed line at y=1, indicates the normalisation procedure (diagram 3.1) such that any subject in whom the PAR response was facilitated by end fill volume lay above the dashed line, and any in whom PAR response was inhibited/suppressed was below the dashed line. As shown in the graph, those subjects with PARefv > 1 were considered to have good GR, and those subjects with PARefv < 1 were considered to have poor GR.

The graph shows the mean normalised latency of the pudendo-anal reflex response expressed as the [mean-1] σSD tested during voiding in non-SCI subjects or neurogenic detrusor overactivity (NDO) in the case of the two SCI groups.

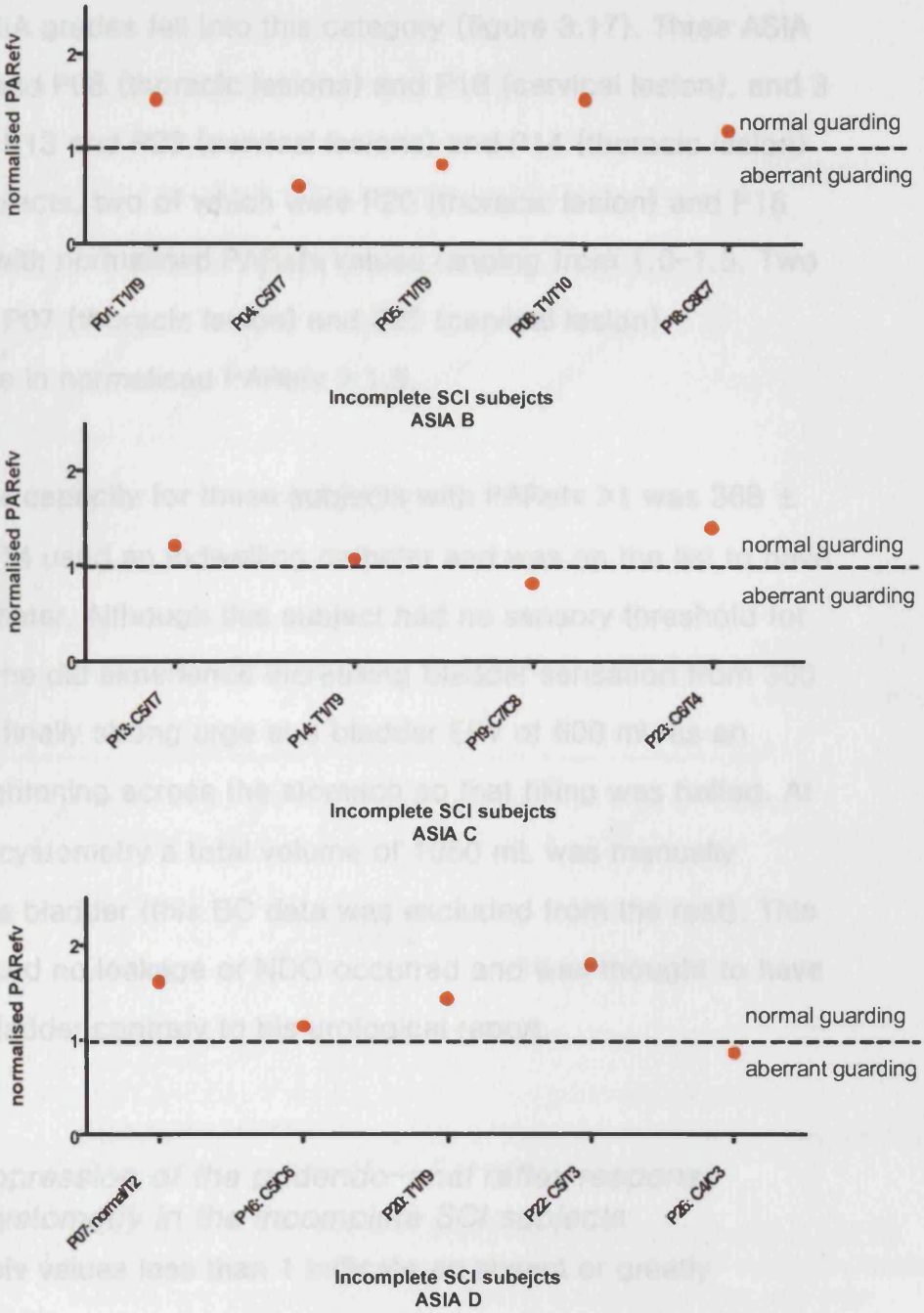


Figure 3.17 **Modulation Of The Normalised Pudendo-Anal Reflex Responses With Filling Cystometry In Incomplete SCI Subjects**

The graphs shows the normalised PAR responses tested at end fill volume representing the guarding responses in iSCI subjects graded ASIA B, C and D and tagged with P followed by a numerical digit with their neurological level of injury (NLI: motor/sensory) thereby preserving anonymity. The dashed line at y=1, indicates the normalisation procedure (diagram 3.1) such that any subject in whom the PAR response was facilitated by end fill volume lay above the dashed line, and any in whom PAR response was inhibited/suppressed was below the dashed line. As shown in the graph, those subjects with PARefv > 1 were considered to have good GR, and those subjects with PARefv < 1 were considered to have poor GR.

subjects of all ASIA grades fell into this category (figure 3.17). Three ASIA B subjects, P01 and P08 (thoracic lesions) and P18 (cervical lesion), and 3 ASIA C subjects: P13 and P23 (cervical lesions) and P14 (thoracic lesion) and 4 ASIA D subjects, two of which were P20 (thoracic lesion) and P16 (cervical lesion) with normalised PARefv values ranging from 1.0-1.5. Two ASIA D subjects, P07 (thoracic lesion) and P22 (cervical lesion) experienced a rise in normalised PARefv > 1.5.

The mean bladder capacity for these subjects with PARefv >1 was 368 ± 99 mL. Subject P14 used an indwelling catheter and was on the list to have a suprapubic catheter. Although this subject had no sensory threshold for DPN stimulation, he did experience increasing bladder sensation from 300 mL onwards and finally strong urge at a bladder EFV of 600 mL as an uncomfortable tightening across the stomach so that filling was halted. At the end of filling cystometry a total volume of 1050 mL was manually aspirated from his bladder (this BC data was excluded from the rest). This subject experienced no leakage or NDO occurred and was thought to have an acontractile bladder contrary to his urological report.

Inhibition or suppression of the pudendo-anal reflex response bladder filling cystometry in the incomplete SCI subjects

Normalised PARefv values less than 1 indicate an absent or greatly aberrant impaired GR and an inability to maintain continence. Only 29% (4/14) of the iSCI subjects fell into this category which included: 2 ASIA B subjects: P04 (cervical lesion, bladder EFV=100mL) and P05 (a thoracic lesion, bladder EFV=100 mL); 1 ASIA C subject, P19, (cervical lesion, bladder EFV=150 mL) and 1 ASIA D subject, P26, (cervical injury). Subject P26 appeared to have a flaccid/acontractile bladder which manifested as an absence in sensation and/or discomfort during bladder filling. For this category with PARefv < 1 the mean bladder capacity was 133±26 mL -

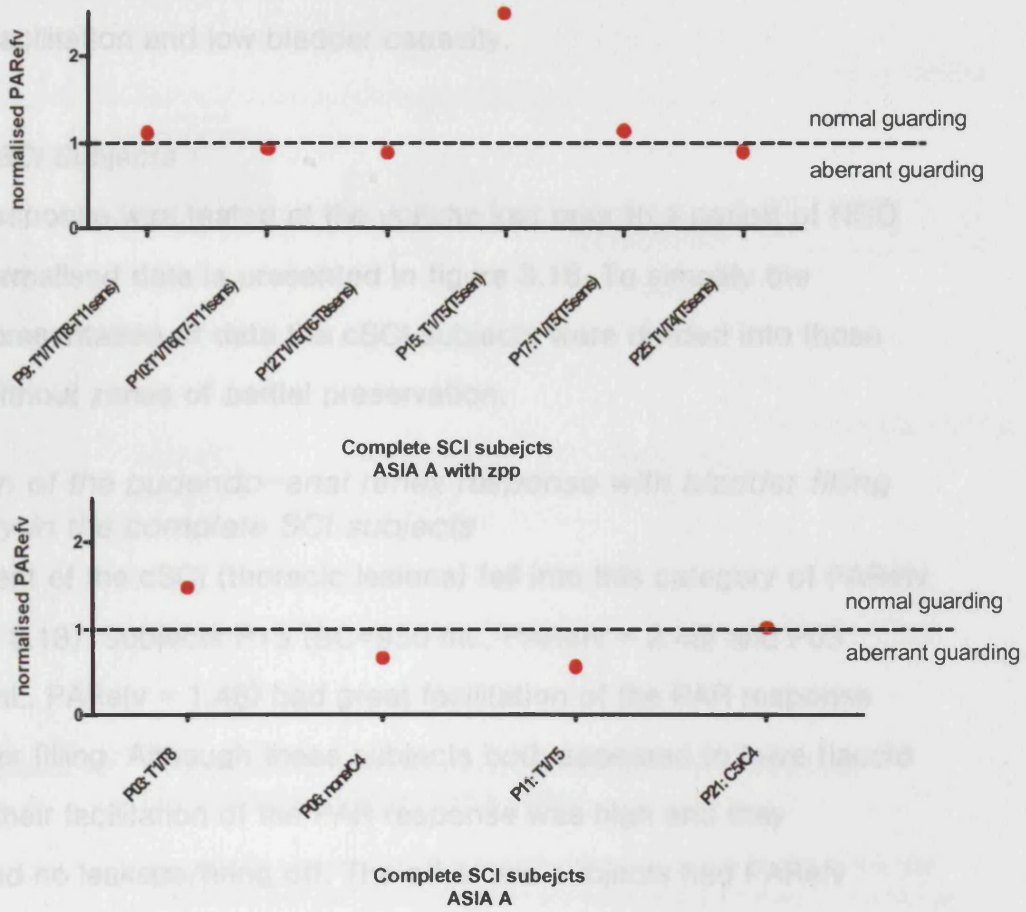


Figure 3.18 **Modulation Of The Normalised Pudendo-Anal Reflex Responses With Filling Cystometry In Complete SCI Subjects**

The graphs shows the normalised PAR responses tested at end fill volume representing the guarding responses in cSCI subjects graded ASIA A and tagged with P followed by a numerical digit with their neurological level of injury (NLI: motor/sensory with zone of partial preservation, zpp, in the top graph, and those with no zpp in the lower graph) thereby preserving anonymity. The dashed line at y=1, indicates the normalisation procedure (diagram 3.1) such that any subject in whom the PAR response was facilitated by end fill volume lay above the dashed line, and any in whom PAR response was inhibited/suppressed was below the dashed line. As shown in the graph, those subjects with PARefv > 1 were considered to have good GR, and those subjects with PARefv < 1 were considered to have poo GR.

implying a possible association between an absence/impairment of PAR response facilitation and low bladder capacity.

Complete SCI Subjects

The PAR response was tested at the volume just prior to a period of NDO and the normalised data is presented in figure 3.18. To simplify the graphical presentation of data the cSCI subjects were divided into those with and without zones of partial preservation.

Facilitation of the pudendo-anal reflex response with bladder filling cystometry in the complete SCI subjects

Forty percent of the cSCI (thoracic lesions) fell into this category of PARefv > 1 (figure 3.18). Subjects P15 (BC=950 mL, PARefv = 2.48) and P03 (BC=550 mL, PARefv = 1.48) had great facilitation of the PAR response with bladder filling. Although these subjects both appeared to have flaccid bladders, their facilitation of the PAR response was high and they experienced no leakage/firing off. The other two subjects had PARefv responses only marginally greater than 1 (P09: BC=370 mL, PARefv = 1.11; and P17: BC=116 mL, PARefv = 1.13). Interestingly in these subjects PARefv manifested very differently with regards to their bladder capacities. These subjects with PARefv > 1 manifested an average bladder capacity 243±179 mL excluding those subjects with low compliance caused by flaccid bladders.

Inhibition or suppression of the pudendo-anal reflex response bladder filling cystometry in the complete SCI subjects

Normalised PARefv values less than 1 indicate an absent GR and an inability to maintain continence during bladder filling. In this category were fifty percent of the cSCI subjects: P10 (BC=80 mL), P12 (BC=170 mL), P25 (BC=230 mL) and P11 (BC=237 mL) (thoracic lesions) and P06 (BC=500 mL, cervical lesion), fell in this category. The average bladder capacity

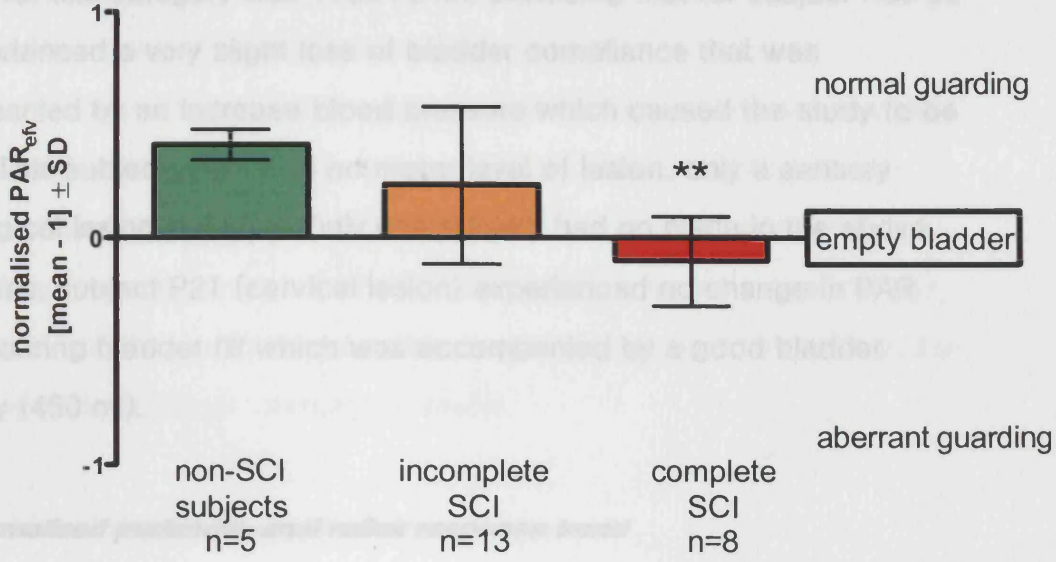


Figure 3.19 Averaged Normalised Pudendo-Anal Reflex Response Modulated By Filling Cystometry

The graph shows the mean normalised changes in the pudendo-anal reflex at end fill volume expressed as the [mean – 1] ο SD at end fill volume in non-SCI (green bar) and the two SCI groups.

Subjects in whom the PAR response was facilitated by end fill volume lay above the x-axis, and any in whom PAR response was inhibited/ suppressed was below the dashed line. As shown in the graph, those subjects with $PAR_{efv} > 1$ were considered to have a good bladder sphincter relationship resulting in an efficient guarding response, and those subjects with $PAR_{efv} < 1$ were considered to have a compromised bladder sphincter relationship resulting in a poor or absent guarding response.

Subjects with a complete spinal lesion have little or no guarding reflex (red bar) compared to non-SCI subjects (denoted by **, p =0.001) whereas incomplete subjects (orange bar) have a preserved but very variable reflex. This variability probably reflects the wide range of neurological impairment in incomplete subjects.

volume for this category was 179±72 mL excluding that for subject P06 as he experienced a very slight loss of bladder compliance that was accompanied by an increase blood pressure which caused the study to be halted. This subject, P06, had no motor level of lesion, only a sensory neurological lesion level C4. Only one subject had no place in the above categories, subject P21 (cervical lesion) experienced no change in PAR activity during bladder fill which was accompanied by a good bladder capacity (450 ml).

The normalised pudendo-anal reflex response trend

Figure 3.19 shows a compilation of the average normalised PAR responses for subjects groups (along the y-axis is the mean-1, such that facilitation of the PAR response is above the x-axis). In non-SCI subjects the averaged normalised PARefv was 1.4 ± 0.06 and indicated the presence of good bladder sphincter coordination, resulting in competent guarding responses that produced high bladder capacities (BC 656±62 ml) with no leakage/incontinence. [Results not included here have shown that when the subject was supine the PAR response remained unchanged over the whole bladder fill, with no increase in EMG activity even at EFV]. The averaged normalised PARefv values in the 14 iSCI subjects was just greater than 1 (PARefv of 1.18±0.4, p=0.14), showing great variability across this group indicating that although the integrity of the GR in this group was often preserved, it was also very variable. Interestingly the averaged normalised PARefv for the 10 cSCI subjects appear to undergo a suppression/ inhibition due to bladder filling (PARefv 0.90±0.19, p=0.001) and was shown to be significantly different in comparison to the averaged PARefv in 5 non-SCI subjects indicating that as a group these cSCI subjects had not preserved the GR.

3.3.5 Repeatability studies

Repeatability during a single visit

Figure 3.20 shows the two PAR values recorded for two separate bladder fills at end fill volume. When the data from both iSCI and cSCI subjects was pooled and statistically analysed high ICC values were obtained [intra-class correlation (ICC) PARefv ICC = 0.80]. This indicated that the parameter, PARefv, could be recorded in consecutive bladder fills with the confident expectation of consistent results.

Repeatability between separate visits

Subjects P10 (T1/T6 ASIA A), P11 (T1/T5 ASIA A), P17 (T1/T5 ASIA A) P18 (C8/C7 ASIA B), P19 (C7/C8 ASIA C), P22 (C5/T3 ASIA D) and P25 (T1/T4 ASIA A) were able to visit the laboratory more than once to test the repeatability of the kinesiological evoked PAR at end fill volume (figure 3.21). Statistical analysis of this data obtained an intra-class correlation for PARefv of ICC = 0.92. This indicated that the PARefv parameter could be repeated very confidently in all these patients.

3.3.6 Bladder capacity

On pooling bladder capacity data with PARefv data (figure 3.22), the SCI subjects fell into a separate cluster with a weak GR that was demonstrated by significantly low bladder capacities associated with significantly low PARefv when compared high integrity GR in non-SCI subjects. The Spearman correlation coefficient, rs = 0.51 (95% confidence interval -0.01 to 0.81) for this data indicated a significant (p=0.04) positive relationship between the PARefv and the bladder end fill volume reflecting a scenario whereby a high integrity GR appears to be associated with a high bladder end fill volume.

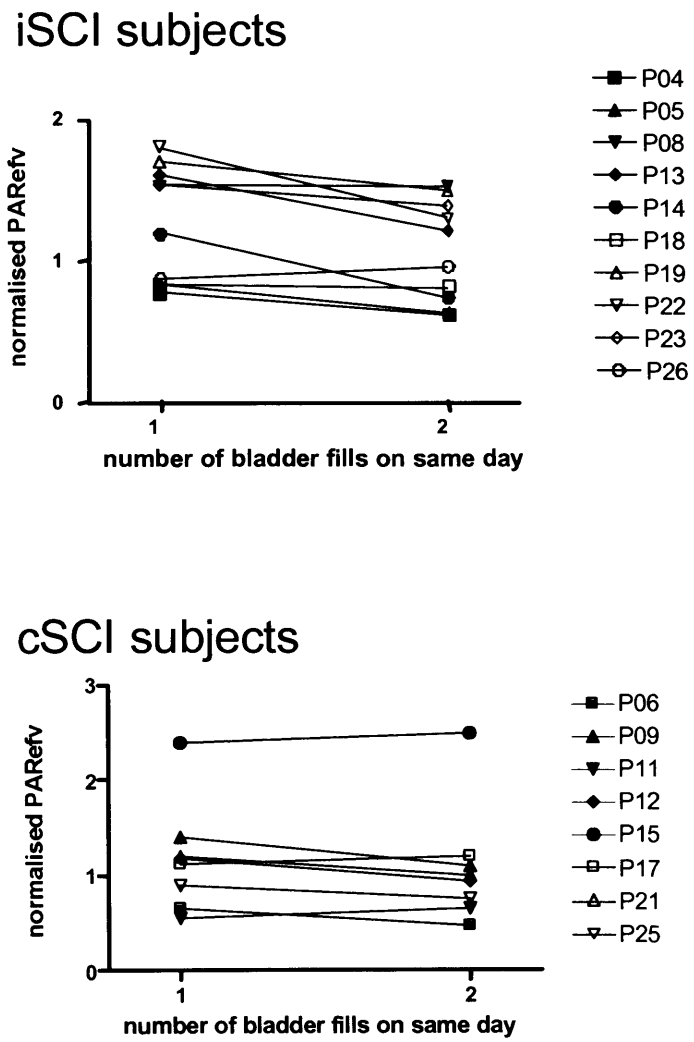


Figure 3.20 Data Recorded From 2 Separate Bladder Fills During One Laboratory Visit In SCI Subjects

When all SCI PARefv data was pooled with to test repeatability the intra-class correlation (ICC) was 0.80 indicating good repeatability

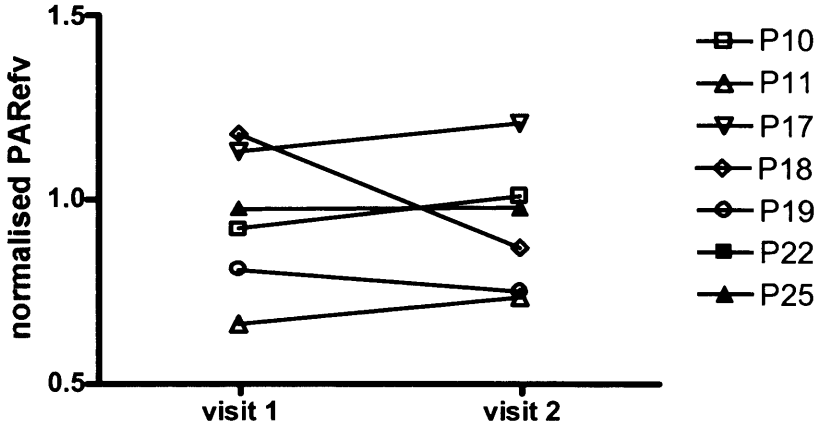


Figure 3.21 Pudendo-Anal Reflex Responses During Filling Cystometry Recorded For Two Separate Visits To The Laboratory In SCI Subjects

Two measures for this parameter were taken on 2 separate visits to the laboratory by the subject.

Statistical analysis gave rise to an intra-class correlation of:
ICC for PARefv = 0.92 indicating very good repeatability for this parameter.

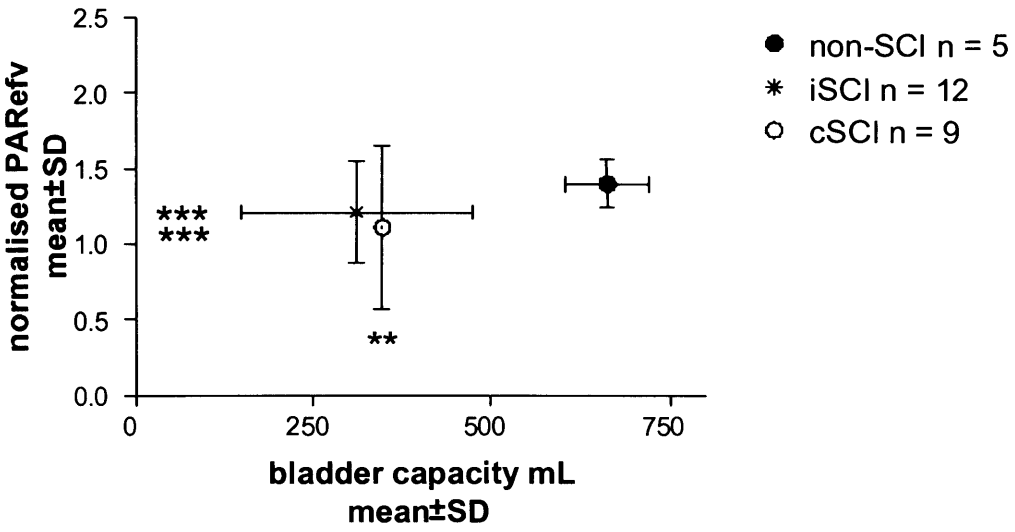


Figure 3.22 Separate Clusters For High And Low Integrity GR

Those with SCI have smaller guarding responses (as indicated by size of PARefv) and bladder capacity suggesting that the presence of little reflex inhibition of the detrusor (that is, NDO occurs at low bladder volumes). Significance, $p = 0.002$, is denoted with ** for PARefv and for bladder capacity with *** denoting $p < 0.0001$ for the iSCI and *** denoting $p = 0.001$ for the cSCI when compared to the non-SCI subject bladder capacity data. 3 subjects were excluded from this analysis as all had flaccid bladders (iSCI: P26, P14 and cSCI: P15)

3.4 Discussion

The hypothesis addressed here was *'the sacral reflex, the PAR, can be used as a measure of the integrity of the guarding response'*. To do this the evoked PAR was tested in both non-SCI and SCI subjects with filling cystometry.

3.4.1 General parameters

The sensory DPN stimulation threshold correlated well with the degree of neurological impairment regardless of the anomalies which existed within the data. That one of the iSCI subjects had no sensory DPN threshold and that one of the cSCI subjects had a sensory threshold shows the variation that exists among these subjects and highlighted early on in this study the deficiencies inherent in the ASIA as a standard neurological assessment.

The DPN stimulation needed to elicit the PAR was similar in non-SCI and iSCI subjects and was greater but not significantly so in cSCI subjects. The higher average reflex threshold for the cSCI subjects could be attributed to the high reflex threshold (70mA) for subject P15 for whom it was only possible to elicit a response at this stimulation. Greater neurological impairment was associated with increased working DPN threshold. This was probably attributable to the fact that it was only the cSCI subjects who could tolerate the high stimulations associated with the 'twice the motor threshold' criteria for DPN stimulation employed.

3.4.2 Optimisation

Single pulse DPN is an unreliable predictor of complete sacral reflex arc lesion whereas double pulse (paired pulse) stimulation has been shown to give reproducible reflex responses (Rodi and Vodusek 1995). The current study investigated the motor evoked potential of the PAR reflex response, optimised by computer averaging of 10 optimised paired-pulses with

bladder function, as a measure of the integrity of the guarding response in non-SCI and SCI subjects. Our findings support those of Rodi and Vodusek (1995) who found that eliciting the optimal recruitment of the pudendo-anal reflex was achieved with a pulse interval of 3ms -which we found in non-SCI subjects. Optimal recruitment in SCI subjects was elicited with a PI of 2ms.

The PAR has proved to be one of the most convenient and useful sacral somatic reflexes to test, especially so in those with neurogenic micturition disturbances and by combining the evoked PAR response measurement with urodynamics we have demonstrated interactive effects of the pelvic afferent activity from the bladder on the sphincters.

3.4.3 Latency

Latency is a good indicator of an efficiently functional pathway. The bulk of neurophysiological studies performed in the past, in the majority, look at the latency of the sacral reflex response (e.g. Dyro and Yalla 1986, Krane and Siroky 1980, Rodi and Vodusek 1995). Surprisingly findings here show the latency of the PAR response to be unrelated to either bladder function or degree of neurological deficit; this may reflect differences in methodology (plug electrode) and smaller sample sizes. It is known that the latency of an evoked response will vary with different strength stimulation. As stimulation strength is increased, there is a decrease in latency due to an increased number of fast sensory fibres being activated. In this study the stimulation used to elicit the PAR response was very variable across the total subject group, which could be considered to be causal in the variation in latency of the PAR response rendering it, even as a normalised parameter, unworthy of consideration in this study.

3.4.4 The Guarding Response

As the bladder fills, related ascending pelvic afferent nerve activity can give rise to a tendency for spontaneous reflex contractions of the detrusor smooth muscle in the bladder wall. However during filling the guarding response (GR) (Garry et al. 1959 (cat); Siroky and Krane, 1981;Park et al, 1997) prevents leakage by producing a progressive involuntary (no sensory awareness) increase in sphincter activity that manifests as increasing sphincter contraction via a pelvic afferent to pudendal efferent reflex. Craggs and McFarlane (1999) suggested that these sphincter contractions (the GR) probably inhibits any tendency for aberrant parasympathetic reflex activity within the spinal cord reducing the possibility of inadvertent detrusor contractions, and later Yoshimura et al, (2004) suggested this inhibition resulted from a combination of sympathetically mediated reflexes controlling the parasympathetic pathway at the pelvic plexus level and contraction of the smooth muscle of the bladder neck and proximal urethra, which would suppress premature voiding/firing off/leaking- hallmarks of incontinence.

Thus the maintenance of continence is achieved by competent urethral closure together with detrusor inhibition resulting from the activation of a number of lumbo-sacral reflex pathways during bladder filling. There is also thought to be an inhibitory feedback reflex mechanism whereby the pudendal efferents inhibit the pelvic afferents at the sacral spinal level resulting in stopping the bladder from contracting at low volumes. Suprasacrally, the bladder filling induced ascending pelvic afferent activity is routed to those parts of the brain (e.g. hypothalamus pre-optic area) detecting sensation, including the PAG in the brain stem (perception of bladder filling) which specifically projects onto the M-nucleus/region of the pons. The drive to the L-nucleus of the pons is unknown as yet and it has been shown to be anatomically unrelated to the M-nucleus (Blok et al.

1997). However it is the L-nucleus that provides an excitatory descending drive to Onuf's nucleus that activates the pudendal efferents to maintain tonicity of the EUS throughout. Bladder fullness coincides with the onset of sensory threshold awareness and sphincter contraction peaks before the onset of micturition becoming a conscious voluntary phenomenon.

Interestingly, recent neurophysiological testing of the pathways of a similar reflex (bladder-anal) has revealed a long latency of around 90 milliseconds (Basinski et al, 2003) suggesting that the guarding response probably involves many interneurones in its arc and could even engage a supra-spinal pathway (Park et al, 1997). Accumulating evidence indicates the presence of a variety of interneuron populations in the sacral circuitry participating in the coordination of activity in parasympathetic bladder efferents with that of the striated urethral sphincter motorneurones (Shefchyk 2001).

Non-SCI subjects

Intact neurological pathways of the non-SCI subjects were demonstrated by their normalised PAR response at end fill volume values being greater than 1. Their good GR manifested as the maintenance of continence and high bladder capacities which were further supported by the maximum scores in the motor and sensory components of the ASIA/IMSOP assessment scale.

Incomplete SCI subjects

This study found that a high percentage (70%) of the iSCI subjects had preserved functional GR (PARefv >1)which maintained continence throughout bladder filling cystometry. This finding was very comparable to the 90% of iSCI subjects with a preserved GR in the Siroky and Krane (1982) study (N=32).

Spinal injury resulting in a loss of descending excitatory modulating influences to Onuf's nucleus would lead to the patient presenting with a poor or absent GR and a loss of reflex inhibition of detrusor activity during filling cystometry, leading to NDO and poor bladder capacity. Twenty-nine percent of the iSCI subjects had a PARefv<1. Generally the GR in the iSCI subjects was found to be preserved similar to those in the non-SCI subjects however it was accompanied by a great deal of variability across this group due to varying degrees of impairment which manifested as much lower bladder capacities.

Complete SCI subjects

Only a small fraction of this group of cSCI subjects had a preserved GR (PARefv > 1) that maintained continence during bladder filling supporting findings by Siroky and Krane (1982). The higher PARefv values were upheld by higher bladder capacity volumes for the most part. However subject P17 had an unexpectedly smaller bladder capacity, which is incongruous with the increased PAR activity at end fill volume. The reason for this might be that although PAR activity increased it was not sufficient to inhibit aberrant detrusor contractions which resulted in the smaller BC.

In a large proportion of these cSCI subjects the GR (PARefv < 1) was absent and their bladder capacities severely diminished, this might result from a loss of descending excitatory modulating influences to Onuf's nucleus. However only in one subject was the bladder capacity incongruously high, mis-matching with his very low PARefv- this was thought to be due to the slight loss in bladder compliance.

This cSCI subject presenting with a cervical lesion experienced no change in the PAR response at EFV but had however a healthy bladder capacity volume, which may suggest a dysfunction in either the feedback of the

bladder afferent system or/and a non-responsive static sphincter efferent system.

By cutting off the descending excitatory modulating influences from the L-nucleus to Onuf's nucleus in the sacral cord poor or absent sphincter guarding responses would be expected with the loss of reflex inhibition of detrusor activity during the filling phase (Park et al, 1997). Therefore, it is believed that the partial preservation or loss of the guarding response, in response to bladder filling, would be an indication of the completeness of spinal injury.

It has recently been discovered that whilst an analogous bowel "guarding response" during rectal filling exists it appears to be present irrespective of spinal cord injury (Chung et al, 2004) therefore showing no significant correlation with completeness of lesion unlike the bladder guarding response. Perhaps this is a reflection of the greater dependence on automatic control in bowel function; the guarding response requiring only sacral segmental control. Or however this may be due to experimental disparities in inclusion criteria: in this current study only subjects with T10 and above lesions were included, whereas in the bowel study there was no cut off limit incorporated in the exclusion criteria – all levels of SCI were included, with their greater varying urological profiles.

3.4.5 Bladder sensation

For the lower urinary tract, the effect of a complete spinal cord lesion is to block ascending afferent activity from the bladder or urethra reaching the brain-stem peri-aquaductal gray during filling and prevent proper pontine coordination of the bladder and sphincters. In fact, all sensations from the lower urinary tract, bowel, pelvic floor and sphincters would be absent as a result of such a lesion and this would include other proprioceptive

pathways normally linking the pelvic floor more directly with the somato-sensory cortex. The loss of pelvic sensation is, perhaps, one of the most disabling features of spinal cord injury. Anecdotal evidence from those complete SCI subjects assessed in this study was that several experienced sensations they described as pain, tension or burning sensation rather than a desire to void, toward the end of a bladder fill. This observation supports those of Ersoz and Akyuz (2004) who also found preservation of bladder sensation in 38.9% of the patients with complete lesions above the spinal level of sensory innervation of bladder (above T11). Hypogastric nerve (T11-L2) is the most proximal sensory innervation of bladder with respect to spinal level. Ersoz and Akyuz (2004) explained the preserved bladder-filling sensation in patients with complete lesions above T11 by the assumption that some neurological tracts in the spinal cord that carry bladder-filling sensation and are different from the ones that carry pinprick and light touch sensations may be spared in SCI patients. Komisaruk et al (1997) showed in women who had T10 and above SCIs a perceptual response to vaginal and/or cervical self-stimulation which was quantified as magnitude of analgesia to calibrated finger compressive force. It would be interesting to look into this further by combining the verbal description of sensation confined to end fill volume with sensory urge scores.

3.4.6 Bladder capacity

Bladder capacity, when paired with normalized PARefv values, the SCI subjects separated into a cluster with weak guarding responses and low bladder capacities resulting from weak pudendal inhibition of aberrant detrusor contractions.

3.4.7 Repeatability

Good repeatability was found for PARefv for separate bladder fills on the same day and different days lending weight to the reliability of this

technique to assess changes in GR if an intervention was given. Significant reproducibility of the data presented here is supported by Rodi and Vodusek (1995) who found double pulse stimulation to be a reliable predictor of complete sacral reflex arc lesions, giving reproducible sacral reflex responses.

3.5 Conclusion

We have used the combined evoked PAR response with urodynamics as a sensitive neurophysiological somato-visceral measure of the integrity of the pathways of the GR involved in the maintenance of continence and have illustrated a relationship between it and the completeness of the spinal cord injury. Although it is unknown as yet, whether it is the afferent or efferent limb that is aberrant, via the examination of the viscero-somatic interaction of sacral reflexes in SCI, we can now assess whether a SCI has an impaired or absent GR- which may eventually lead to the development of a sensitive tool with which we can determine more precisely the changes of sacral segmental reflexes following biological interventions such as neural repair.

Chapter 4

Modulation Of The Bladder Guarding Response During Voiding Cystometry

4.0 Introduction

Normal voiding requires good bladder sphincter coordination, such that the guarding response (GR) is 'switched off', allowing unobstructed voiding. Damage to the spinal cord can lead to impaired /uncoordinated / dyssynergic bladder and sphincter function and the emergence of aberrant reflex activity. In detrusor sphincter dyssynergia (DSD) , the detrusor and urethral sphincter contract simultaneously rather than reciprocally resulting in obstruction of the urethra and decreased flow from the bladder (Blaivas et al., 1981; Siroky and Krane, 1982; Galeano et al., 1986; Rudy et al., 1988; Sethi et al., 1989; Chancellor et al., 1990; Kruse and de Groat, 1990; Madersbacher, 1990; Walter et al., 1994; Pikov and Wrathall, 2001). Dyssynergia leads to incomplete bladder emptying and high intravesical pressures which in turn are linked to the deterioration of the upper urinary tract.

4.1 Aim

The aim of this study was to investigate whether the aberrant sacral reflexes that emerge with spinal cord injury (SCI) alter the subjects' ability to suppress or inhibit the GR during voiding or voiding dysfunction. This was done by looking at the modulation of the sacral somatic pudendo-anal reflex (PAR), as a surrogate marker for the pudendo-urethral reflex, during intrinsic bladder emptying, for assessing residual supra-sacral bladder and sphincter function and development of aberrant reflexes in SCI subjects. These techniques will provide a greater understanding of the interaction of the spinal pathways and sacral reflexes on bladder and sphincter function following injury and will be invaluable for optimising and assessing the outcome of future neuroregeneration techniques.

4.2 Methods

In summary, 5 non-SCI subjects, 14 iSCI subjects and 10 cSCI subjects participated in this study. They underwent a neurological examination using the ASIA/IMSOP impairment scoring system. Subjects were then placed in a supine position with electrodes in place for DPN stimulation and pudendo-anal reflex monitoring with a catheter, filling line and pressure line in place for filling the bladder retrogradely from a saline bag attached to an infusion pump and monitoring intravesical pressure to predict neurogenic detrusor overactivity (NDO) respectively in spinal injured subjects. DPN stimulation general parameters were established: sensory, reflex and working thresholds. The pudendo-anal reflex was optimised and tested when the bladder was empty. (Same experimental set up as Chapter 3).

4.2.1 Modulation Of Pudendo-Anal Reflex ($PAR_{void/Ndo}$) Response With Voiding Cystometry

The PAR was tested during voiding in the non-SCI subjects. In the SCI subjects intravesical pressure (Pves) was monitored closely throughout bladder filling as a predictive indicator of an NDO (uninhibited) contraction. Filling was stopped when there was a sustained rise of Pves or when incontinence (firing off) was noted. In those SCI subjects that experienced NDO, with and without DSD, the optimised PAR response was elicited and monitored during NDO ($PAR_{void/NDO}$). Bladder capacity was calculated by taking the sum of the fluid fired off and the residual volume aspirated from the bladder.

4.2.2 Repeatability Testing

Where possible several PARs were elicited within one period of NDO. Pertaining to time and patient comfort the rate of fill was increased from 20 ml/min to 30-50 ml/min in order to perform several bladder fills per visit.

Only in some cases did subjects return to participate on a separate study day.

4.2.3 Criteria For Analysis

Data was analysed using the Spike program. All information was treated confidentially and conformed to the regulations described in the Data Protection Act. All PAR values underwent the normalisation technique. Data was pooled and expressed as a mean ± SD. Clinical statistical significance between SCI and non-SCI subject data was determined with 95% confidence interval using an unpaired 2-tailed t-test with Welch's correction. [The unpaired t test assumes that the two populations have the same variances. Since the variance equals the standard deviation squared, this means that the populations have the same standard deviation). A modification of the t test (developed by Welch) is used when one is unwilling to make that assumption]. Repeatability was assessed using intra subject correlations (also known in the statistical literature as intra-class correlations, (ICCs)). The ICC = the ratio of between subject variance/ to (between subject variance plus within subject variance). A higher ICC (closer to 1) value was associated with better repeatability of the parameter in question.

4.3 Results

4.3.1 Latency Of The PAR Response During Voiding Cystometry

During voiding in the non-SCI subject (figure 4.1) the sphincter EMG was suppressed. The PAR response was tested at this time in non-SCI subjects. The normalised latency of these PAR responses is plotted in figure 4.2. The normalised latencies of the $PAR_{void/NDO}$ responses for the SCI groups were also analysed. Figures 4.3 and 4.4 show normalised latencies of PAR responses during NDO for the iSCI and the cSCI subjects

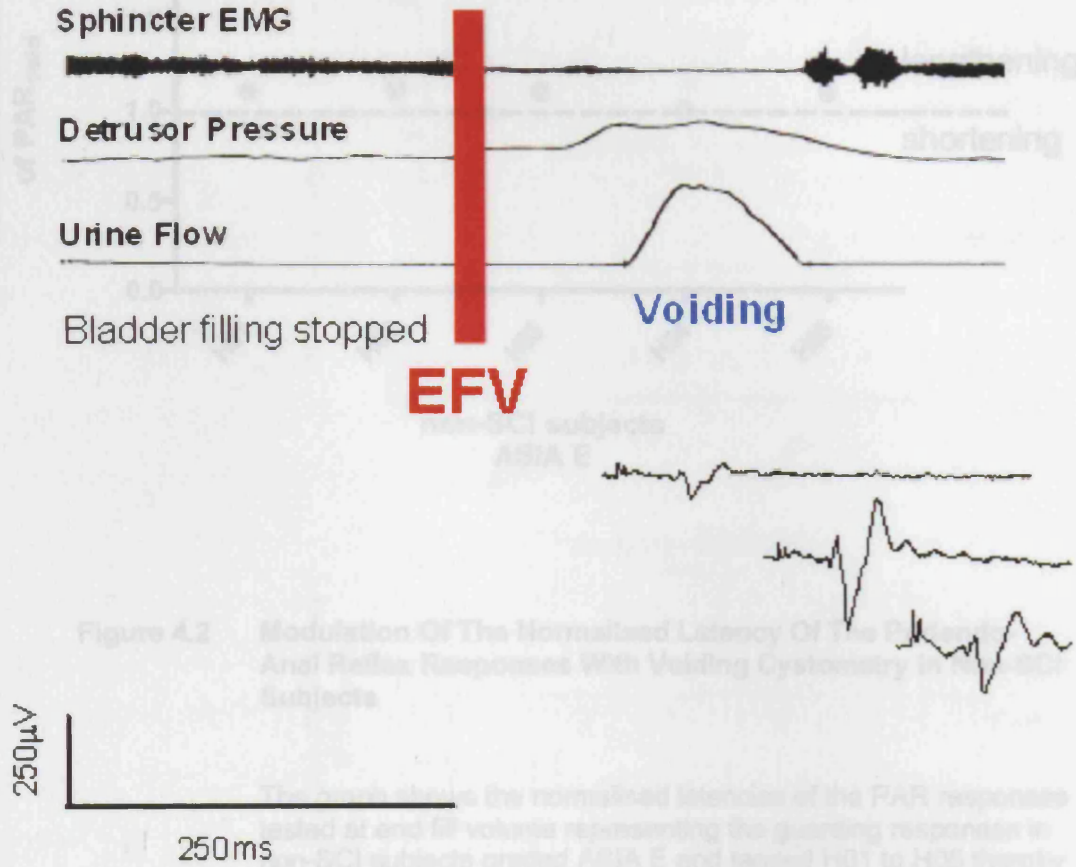


Figure 4.1 Interaction Of The Somatic Pudendal-Anal Reflex Response With The Voiding Cystometry In A Non-SCI Subject

The top trace shows the sphincter EMG which built up to a maximum at the end fill volume (EFV) at which point the guarding response became volitional. PAR activity and sphincter EMG was attenuated during voiding and returned to control values as the bladder began to fill naturally.

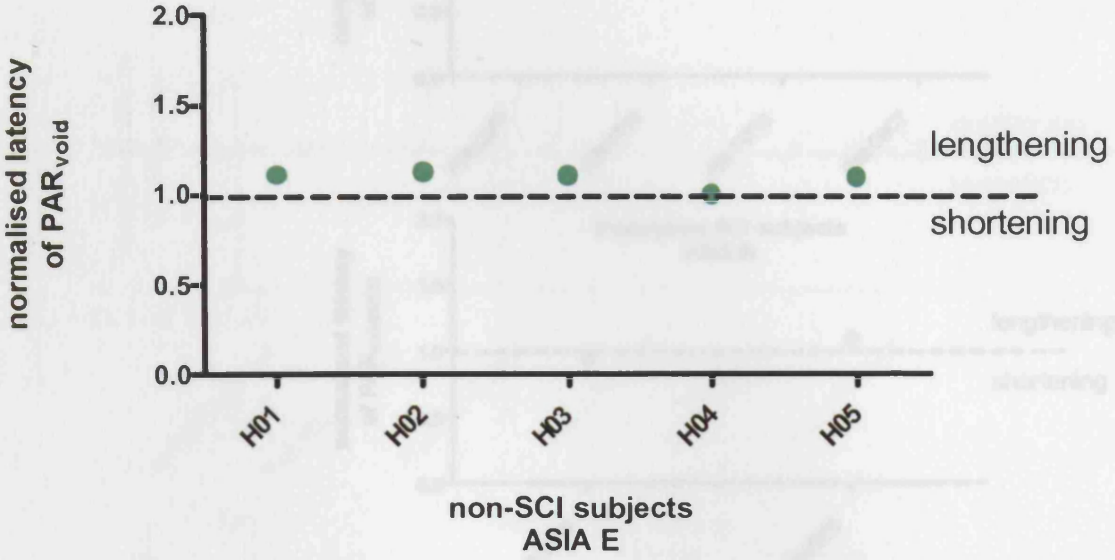


Figure 4.2 **Modulation Of The Normalised Latency Of The Pudendo-Anal Reflex Responses With Voiding Cystometry In Non-SCI Subjects**

The graph shows the normalised latencies of the PAR responses tested at end fill volume representing the guarding responses in non-SCI subjects graded ASIA E and tagged H01 to H05 thereby preserving anonymity. The dashed line at y=1, indicates the normalisation procedure (diagram 3.1) such that any subject in whom end fill volume shortened the latency was above the dashed line, and any in whom the latency was lengthened was below the dashed line.

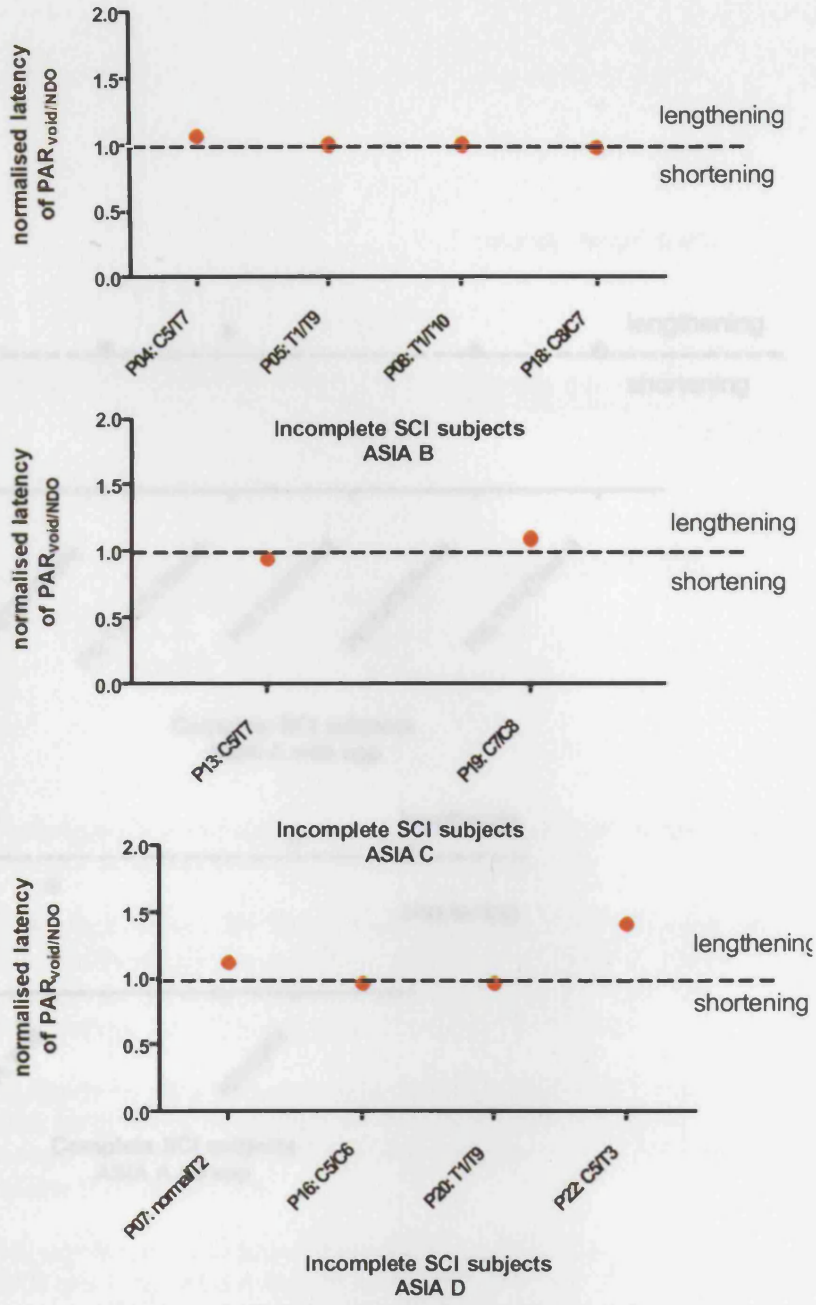


Figure 4.3 **Modulation Of The Normalised Latency Of The Pudendo-Anal Reflex Responses With Voiding Cystometry In Incomplete SCI Subjects**

The graph shows the normalised latencies of the PAR responses tested during voiding and NDO representing the suppression or inhibition of the guarding responses in iSCI subjects (coded with P followed by a numerical digit) graded ASIA B, C and D with their neurological level of injury (motor/sensory) thereby preserving anonymity. The dashed line at y=1, indicates the normalisation procedure (diagram 3.1) such that any subject in whom voiding/NDO shortened the latency was above the dashed line, and any in whom the latency was lengthened was below the dashed line.

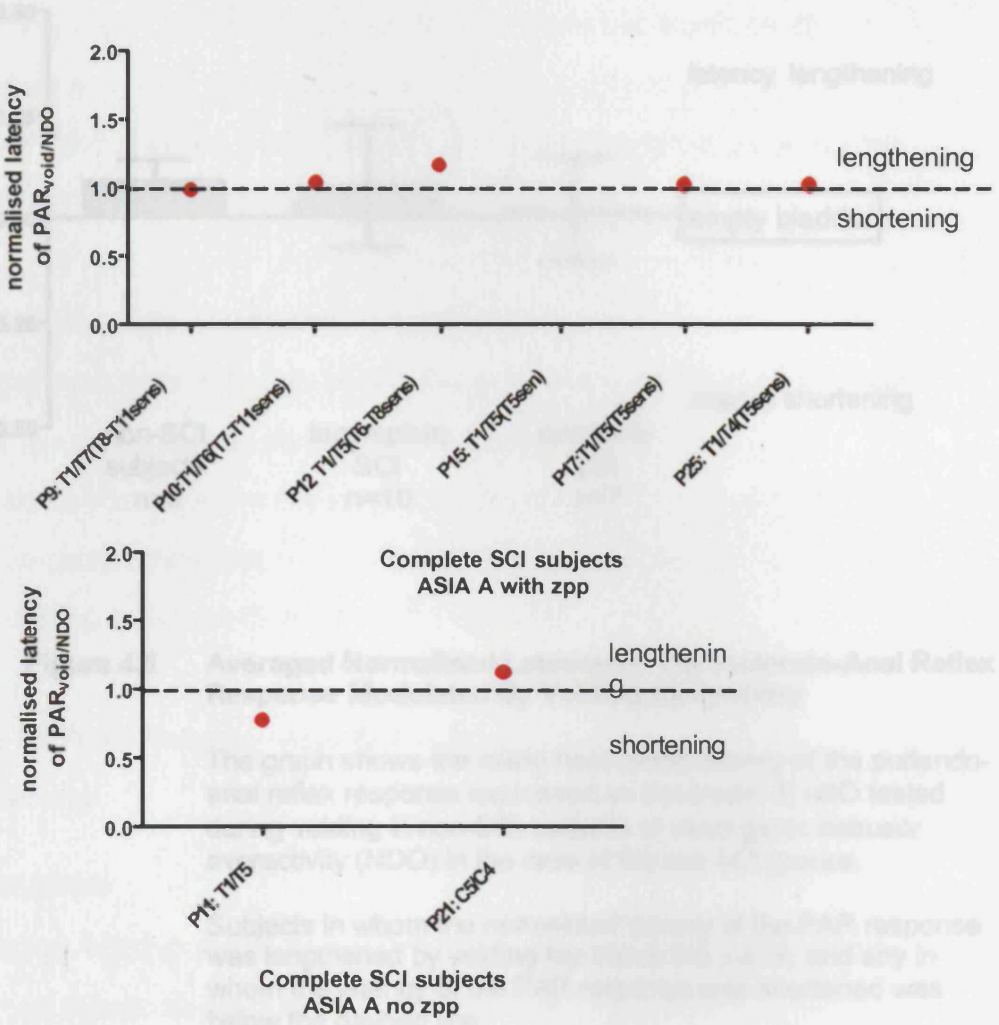


Figure 4.4 **Modulation Of The Normalised Latency Of The Pudendo-Anal Reflex Responses With Voiding Cystometry In Complete SCI Subjects**

The graph shows the normalised latencies of the PAR responses tested during voiding and NDO representing the suppression or inhibition of the guarding responses in cSCI subjects (coded with P followed by a numerical digit) graded ASIA A with their neurological level of injury (motor/sensory, with or without a zone of partial preservation, zpp graph) thereby preserving anonymity. The dashed line at y=1, indicates the normalisation procedure (diagram 3.1) such that any subject in whom voiding/NDO shortened the latency was above the dashed line, and any in whom the latency was lengthened was below the dashed line.

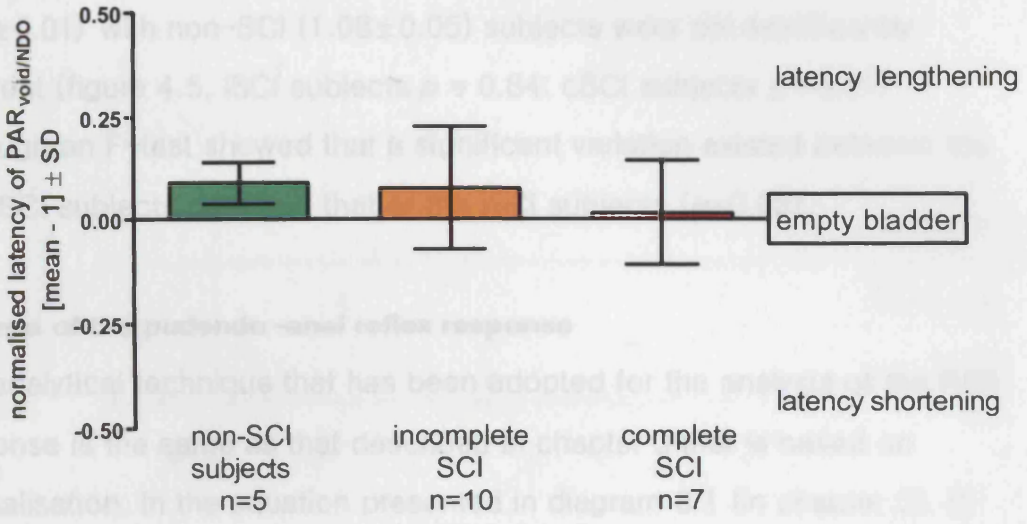


Figure 4.5 Averaged Normalised Latency Of The Pudendo-Anal Reflex Response Modulated By Voiding Cystometry

The graph shows the mean normalised latency of the pudendo-anal reflex response expressed as the [mean-1] ±SD tested during voiding in non-SCI subjects or neurogenic detrusor overactivity (NDO) in the case of the two SCI groups.

Subjects in whom the normalised latency of the PAR response was lengthened by voiding lay above the x-axis, and any in whom the latency of the PAR response was shortened was below the dashed line.

No significant differences between the SCI groups and the non-SCI group appeared to exist with this parameter (iSCI subjects p = 0.84; cSCI subjects p =0.21). Although an F-test did indicate that a significant difference in variation existed between the normalised latency of the PAR response during voiding in non-SCI subjects with that during NDO in this group of iSCI subjects (p = 0.03).

respectively. The mean normalised latencies between the two groups of SCI subjects (iSCI subjects: mean±SD: 1.07±0.07; cSCI subjects 1.01±0.01) with non-SCI (1.08±0.05) subjects were not significantly different (figure 4.5, iSCI subjects p = 0.84; cSCI subjects p =0.21) although an F-test showed that a significant variation existed between the non-SCI subjects data and that of the iSCI subjects (p=0.03).

Analysis of the pudendo-anal reflex response

The analytical technique that has been adopted for the analysis of the PAR response is the same as that described in chapter 3 that is based on normalisation. In the equation presented in diagram 3.1 (in chapter 3), C_T is the peak to peak amplitude of the PAR tested during voiding in non-SCI subjects or during a period of NDO in SCI subjects.

4.3.2 Peak To Peak Pudendo-Anal Reflex Response During Voiding Cystometry

Non-spinal subjects

During volitional voiding in the non-SCI the PAR response was attenuated (figure 4.6- all values being below the dashed line, PARvoid <1). The averaged normalised PAR_{void} was 0.34±0.21 indicating that the GR was suppressed or inhibited sufficiently by bladder sphincter synergistic coordination allowing unobstructed voiding or bladder emptying. The PAR response was then enhanced at 2 min-post void after which it returned to baseline 4 min-post void as the bladder started to fill naturally (figure 4.1).

Incomplete SCI subjects

Facilitation Of Pudendo-Anal Reflex Activity During Voiding Cystometry

Those subjects who experienced relatively high $PAR_{void/NDO} > 1$ (above the dashed line in figure 4.7) were P05 (T1/T9, ASIA D), P13 (C5/T7, ASIA C), P20 (T1/T9, ASIA D) and P22 (C5/T3, ASIA D). Result traces for subject

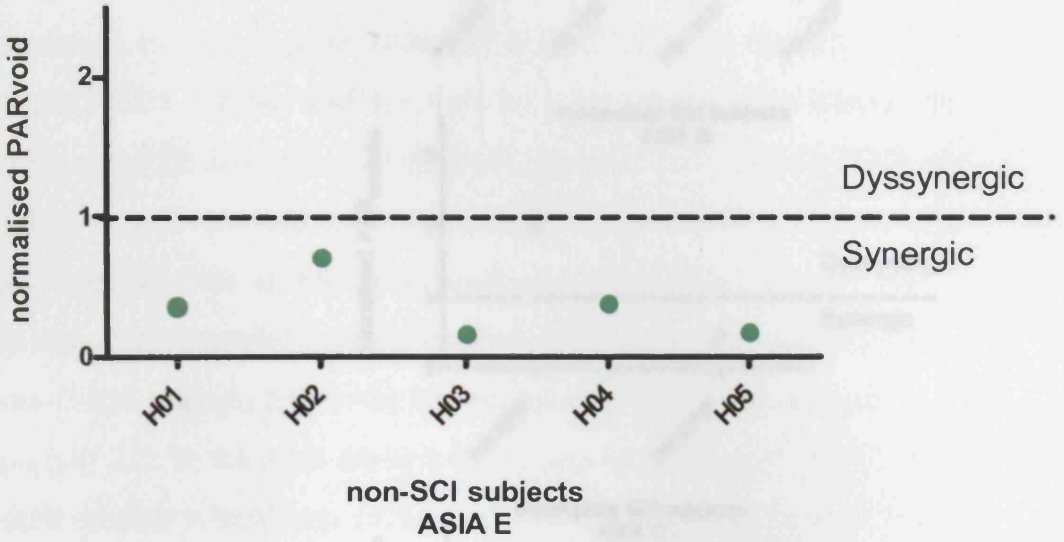


Figure 4.6 **Modulation Of The Normalised Pudendo-Anal Reflex Responses With Voiding Cystometry In Non-SCI Subjects**

The graph shows the normalised PAR responses tested during voiding representing the suppression or inhibition of the guarding response in non-SCI subjects graded ASIA E and tagged H01 to H05 thereby preserving anonymity. The dashed line at y=1, indicates the normalisation procedure (diagram 3.1) such that any subject in whom the PAR response was facilitated by voiding lay above the dashed line, and any in whom PAR response was inhibited/suppressed was below the dashed line. As shown in the graph, those subjects with PARvoid > 1 were considered to have a dyssynergic bladder sphincter relationship resulting in obstructed voiding, and those subjects with PARvoid < 1 were considered to have a synergic bladder sphincter relationship manifesting in normal voiding.

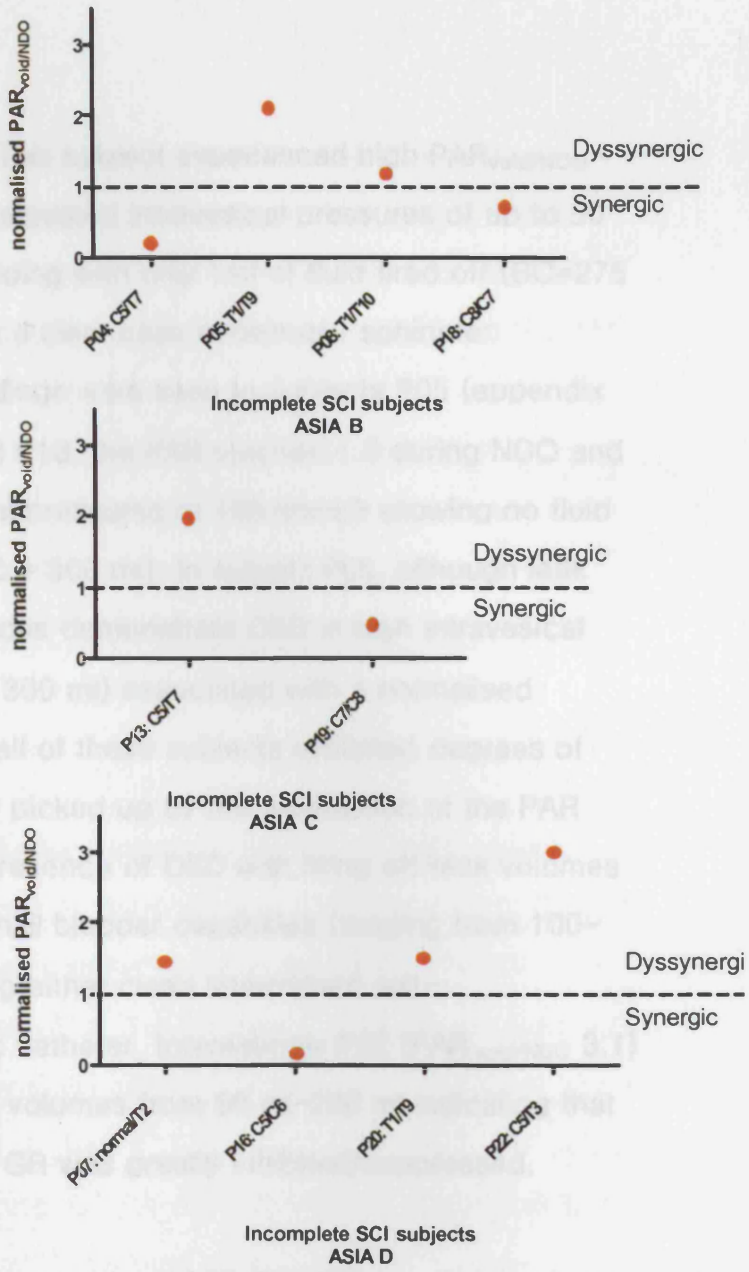


Figure 4.7 Modulation Of The Normalised Pudendo-Anal Reflex Responses With Voiding Cystometry In Incomplete SCI Subjects

The graph shows the normalised PAR responses tested during voiding and NDO representing the suppression or inhibition of the guarding responses in iSCI subjects (coded with P followed by a numerical digit) graded ASIA B, C and D with their neurological level of injury (motor/sensory) thereby preserving anonymity. The dashed line at y=1, indicates the normalisation procedure (diagram 3.1) such that any subject in whom the PAR response was facilitated by voiding lay above the dashed line, and any in whom PAR response was inhibited/ suppressed was below the dashed line. As shown in the graph, those subjects with $PAR_{void/NDO} > 1$ were considered to have a dyssynergic bladder sphincter relationship resulting in obstructed voiding, and those subjects with $PAR_{void/NDO} < 1$ were considered to have a synergic bladder sphincter relationship manifesting in unobstructed voiding.

P20 are shown in appendix 4. This subject experienced high $PAR_{void/NDO}$ = 1.5 which was coincident with elevated intravesical pressures of up to 50 cmH_20, causing obstructed voiding with only 1ml of fluid fired off (BC=275 ml). The results of P20 present a clear case of detrusor sphincter dyssynergia (DSD). Similar findings were seen in subjects P05 (appendix 5) and P13 and P22. In subject P13, the PAR reached 1.9 during NDO and was coincident with intravesical pressures of 100 cmH_20 allowing no fluid at all to leak or be fired off (BC = 300 ml). In subject P05, although leak volumes were not recorded traces demonstrate DSD in high intravesical pressures (>100 cmH_20, BC = 300 ml) associated with a normalised $PAR_{void/NDO}$ of 2.1. In the main all of these subjects exhibited degrees of obstructed voiding which were picked up by the modulation of the PAR response. This indicated the presence of DSD with firing off/leak volumes being very minimal (0-4ml), small bladder capacities (ranging from 100-300 ml) and management being either clean intermittent self-catheterization or a suprapubic catheter. Interestingly P22 ($PAR_{void/NDO}$ 3.1) experienced a range of leaked volumes from 90 ml-200 ml indicating that in between points of DSD, the GR was greatly inhibited/suppressed.

The normalised $PAR_{void/NDO}$ of one subject, P08 (T1/T10) lay slightly above the normalization line at 1.18. Although this subjects' intravesical pressures rose to 100 cmH_20, this was only associated with a relatively small amount of sphincter EMG activity during which a large volume (leaked=150 ml, BC= 320 ml) was fired off. This subject only experienced NDO and no DSD, in accordance with his urological report. The high PARndo value (1.45) in subject P07 (normal/T2 sensory lesion), he said, was to do with inhibition due to his surroundings.

Inhibition Of Pudendo-Anal Reflex Activity During Voiding Cystometry

Subjects falling into this category all had cervical lesions: P04 (PARndo =0.28) and P18 (ASIA B, PARndo = 0.72, 60 mL fired off), P19 (ASIA C, PARndo = 0.47, 100 mL fired off) and lastly P16 (ASIA D, PARndo = 0.16).

In this group of iSCI subjects PARndo was very variable ranging from near normal to grossly aberrant (PARndo/void 1.16±0.99, p=0.01, figure 4.9) and found overall to be significantly different from PARvoid in non-SCI subjects.

Complete SCI subjects

Facilitation Of Pudendo-Anal Reflex Activity During Voiding Cystometry

Subjects P10, P11 and P12 (thoracic lesions) were listed as having DSD in their urological reports. This was well reflected in the values of their PARndo, which were greater than 1 in P10 (PARndo = 1.7, 20 mL fired off), P11 (PARndo = 1.5, 222 mL fired off) and P12 (PARndo = 1.3, 70 mL fired off) (figure 4.8). In the case of subject P11 (refer to appendix 6) the period of NDO experienced was long enough for several PARndo recordings to be elicited, and 222 mL encompasses the total volume leaked, not one volume leaked at the point of PAR elicitation.

Inhibition Of Pudendo-Anal Reflex Activity During Voiding Cystometry

Forty percent (4/10) of these cSCI subjects fell into this category of a drop in PAR activity after EFV. Three out of the 4 subjects had thoracic lesions: P17 (PARndo = 0.59, 30 mL fired off) and P25 (PARndo = 0.56, 50 mL fired off) both had PARndo < 1, P09 (PARndo = 1, 220 mL fired off), the fourth being a cervical lesion, P21 (PARndo = 0.79, 100 mL fired off). The average PARndo in this group of cSCI subjects was very similar to the PARefv of this group (PARvoid/ndo 1.0±0.4, figure 4.9) and found to be significantly different (p=0.005) to the PARvoid in the non-SCI subjects.

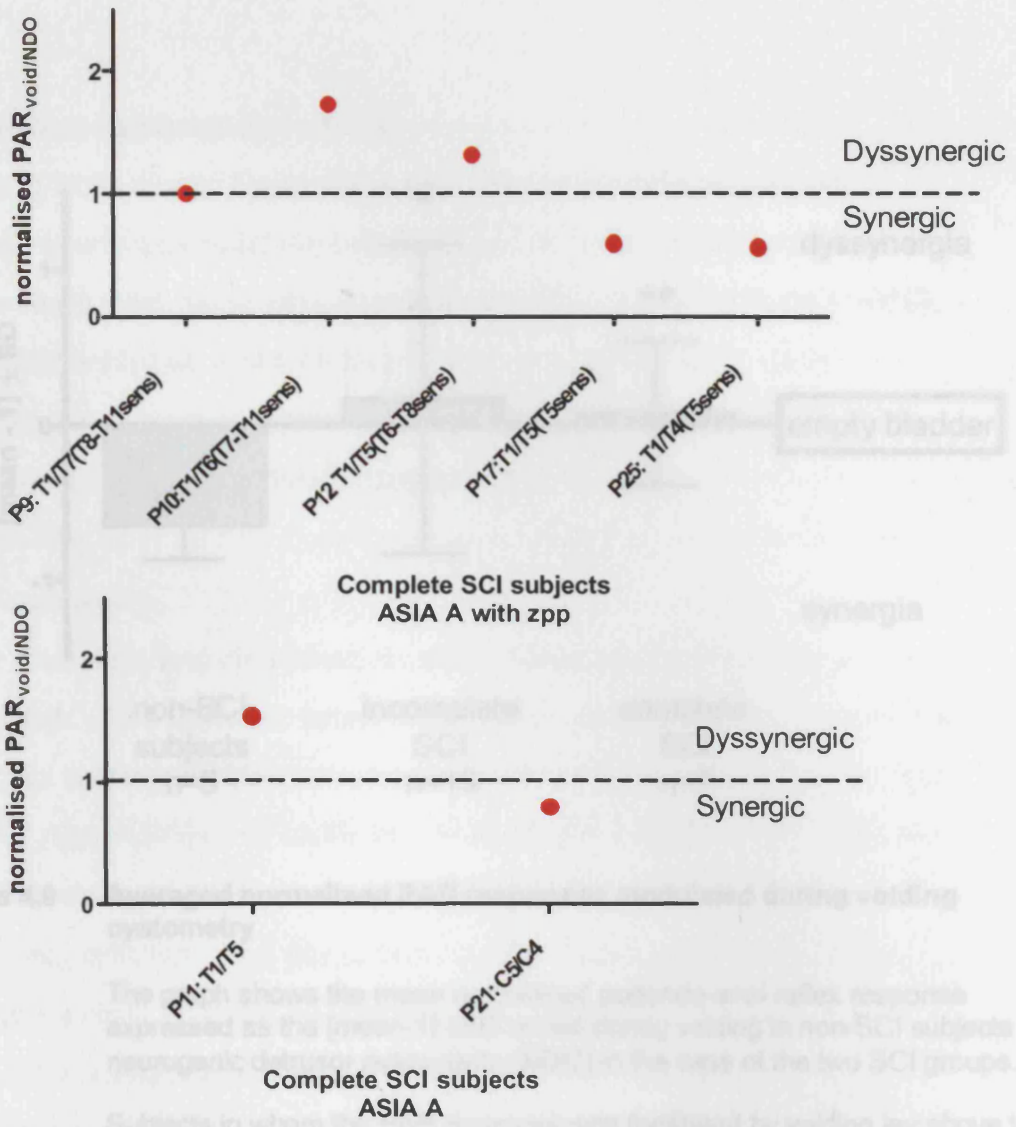


Figure 4.8 Modulation Of The Normalised Pudendo-Anal Reflex Responses With Voiding Cystometry In Complete SCI Subjects

The graph shows the normalised PAR responses tested during voiding and NDO representing the suppression or inhibition of the guarding responses in cSCI subjects (coded with P followed by a numerical digit) graded ASIA A with their neurological level of injury (motor/sensory, with or without a zone of partial preservation, zpp graph) thereby preserving anonymity. The dashed line at y=1, indicates the normalisation procedure (diagram 3.1) such that any subject in whom the PAR response was facilitated by voiding lay above the dashed line, and any in whom PAR response was inhibited/ suppressed was below the dashed line. As shown in the graph, those subjects with $PAR_{void/NDO} > 1$ were considered to have a dyssynergic bladder sphincter relationship resulting in obstructed voiding, and those subjects with $PAR_{void/NDO} < 1$ were considered to have a synergic bladder sphincter relationship manifesting in unobstructed voiding.

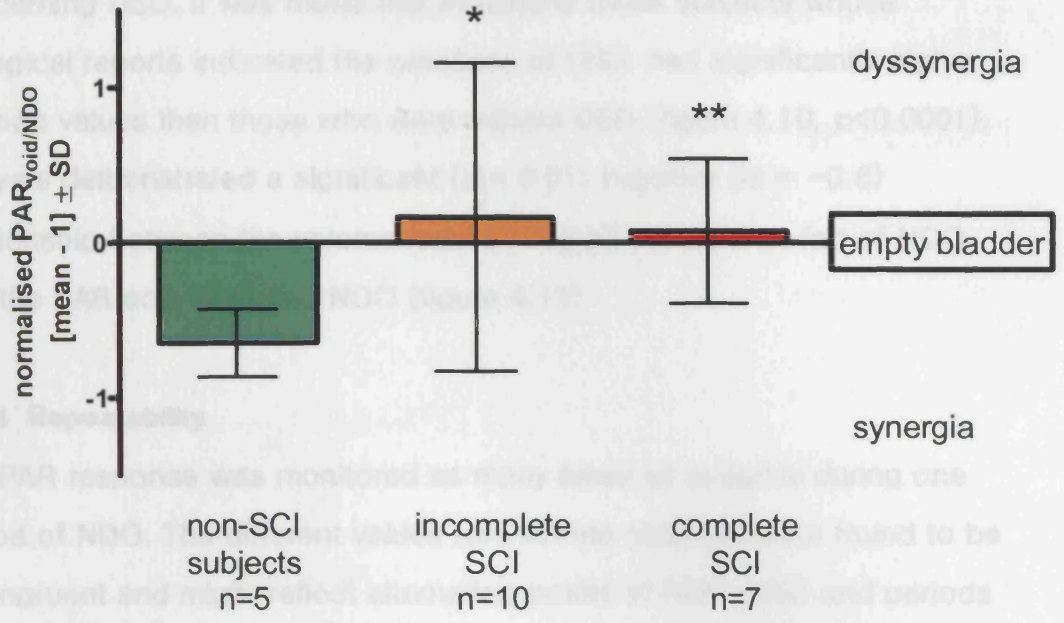


Figure 4.9 Averaged normalised PAR responses modulated during voiding cystometry

The graph shows the mean normalised pudendo-anal reflex response expressed as the [mean-1] ±SD tested during voiding in non-SCI subjects or neurogenic detrusor overactivity (NDO) in the case of the two SCI groups.

Subjects in whom the PAR response was facilitated by voiding lay above the x-axis, and any in whom PAR response was inhibited/ suppressed was below the dashed line. As shown in the graph, those subjects with $PAR_{void/NDO} > 1$ were considered to have a dyssynergic bladder sphincter relationship resulting in obstructed voiding, and those subjects with $PAR_{void/NDO} < 1$ were considered to have a synergic bladder sphincter relationship manifesting in unobstructed voiding (green bar).

In subjects with a spinal injury the PAR response during NDO was significantly different from the PAR during voiding in the non-SCI subjects reflects varying levels of voiding dysfunction including detrusor sphincter dyssynergia (denoted by * p=0.013 for iSCI subjects (orange bar) and ** p=0.005 for cSCI subjects (red bar).

4.3.3 Detrusor Sphincter Dyssynergia

Concerning DSD, it was found that in general those subjects whose urological reports indicated the presence of DSD, had significantly higher PARndo values than those who were without DSD (figure 4.10, $p<0.0001$). Analysis demonstrated a significant ($p = 0.01$) negative (rs = −0.6) relationship between the volume leaked/fired off during a period of NDO and the PAR activity during NDO (figure 4.11)

4.3.4 Repeatability

The PAR response was monitored as many times as possible during one period of NDO. The different values for PARndo obtained were found to be incongruent and might reflect alternating points of NDO, DSD and periods of leaking. Appendices 5-9 show where and how many times the PARndo was elicited during a single period of NDO in 5 SCI subjects. This was found to vary with how long the period of NDO lasted and how fast the investigator was to start the PAR sampling. Data used in the statistical analysis for a subject were either the first PARvoid/ndo sampled or the highest PARvoid/ndo value, which was thought to indicate the presence of DSD.

Only in some subjects was the PAR elicited several times during one period of NDO (figure 4.12: the 8 subjects excluded from this data included those who experienced no NDO, or for whom only a single sample was taken during a period of NDO, or who were too inhibited to void). Subjects P05, P08 and P20 gave fluctuating data, containing both PARndo values of greater and less than 1. Statistical analysis gave rise to a poor intra-class correlation, ICC = 0.30 which can be interpreted as the 2 values for PARndo from one subject vary a good deal in relation to the differences between the subjects. Thus there is poor repeatability between different PARndo values during one period of NDO.

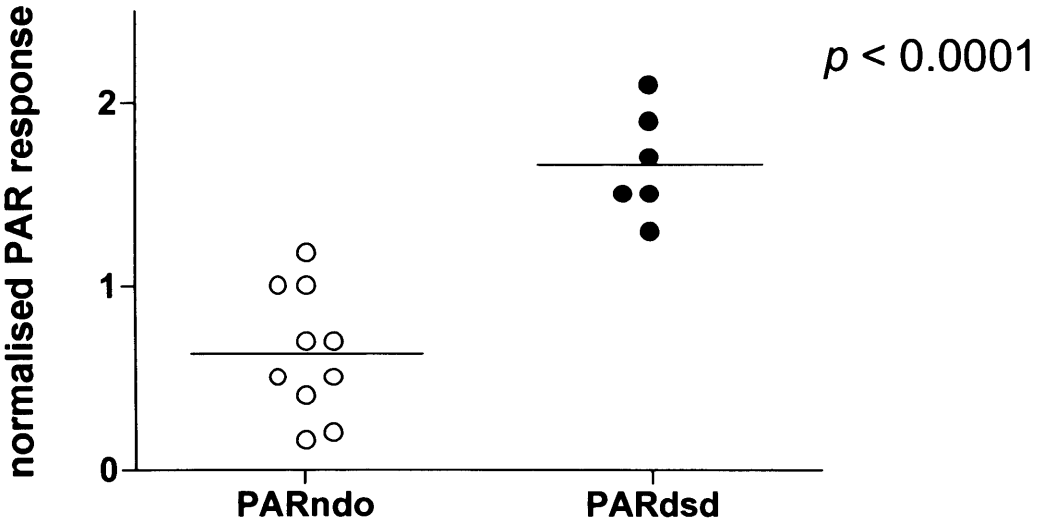


Figure 4.10 Occurrence Of Detrusor Sphincter Dyssynergia

The normalised PAR response recorded during an episode of neurogenic detrusor overactivity (PARvoid/ndo) in patients with and without detrusor sphincter dyssynergia (DSD), as per their urological reports. The p value, $p < 0.0001$, denotes a highly significant difference in PAR during periods of NDO between the two groups.

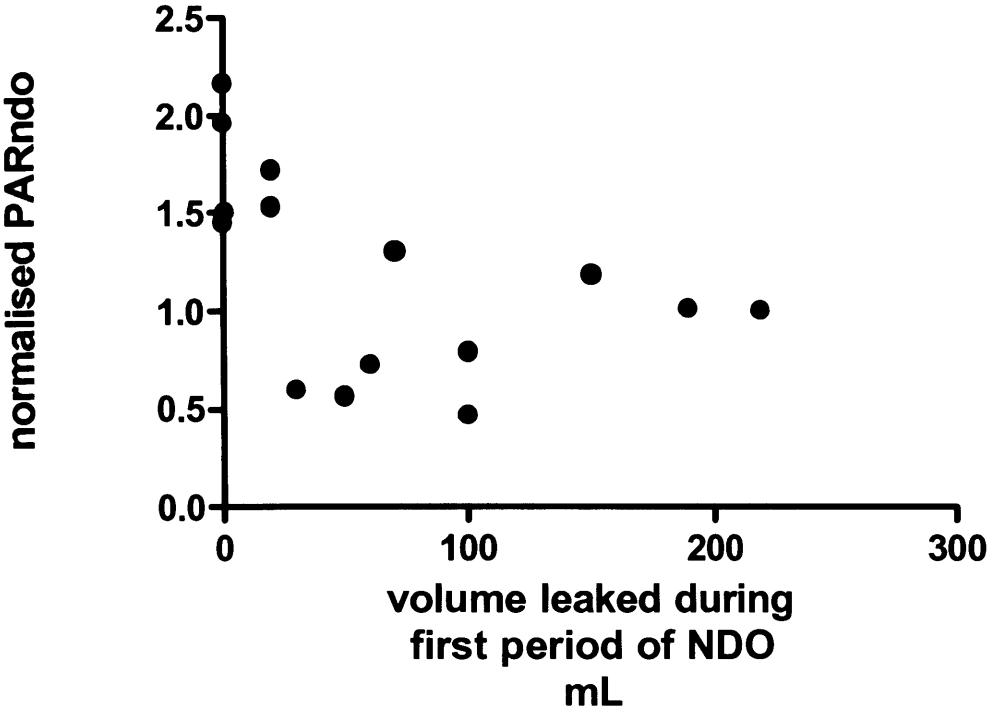


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Figure 4.11 **Correlation Between The Volume Leaked And PARndo**

The parameter, PARndo was elicited during the first period of NDO experienced by the subject, and the volume leaked or fired off by the subject (x-axis) was recorded. The Spearman correlation coefficient, rs = -0.63 (95% confidence interval -0.86 to -0.16) shows that PARndo and the volume leaked/fired off have a significant (p (2-tail) =0.011) negative relationship, suggesting that the lower the PARndo value the greater the volume leaked.

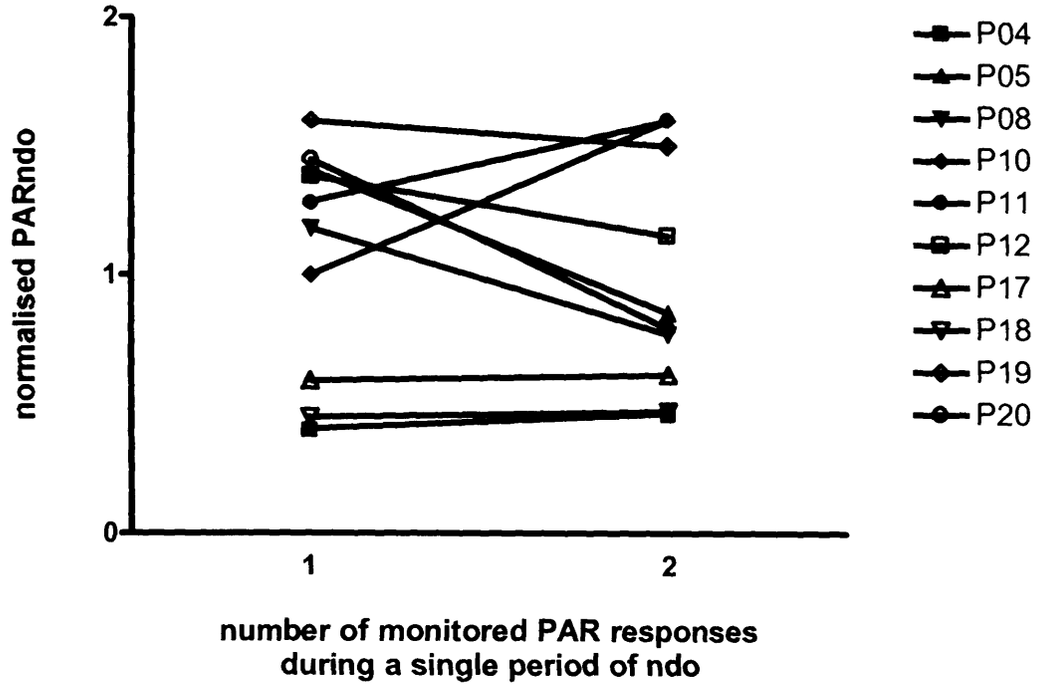


Figure 4.12 **$PAR_{void/NDO}$ Sampling During One Period Of NDO**

Variability was seen here due to intermittent contraction and relaxation of the EAS, which coincided with intermittent firing off. Statistical analysis to test repeatability gave rise to a poor intra-class correlation, ICC = 0.30 indicating poor repeatability between different PARndo values during one period of NDO.

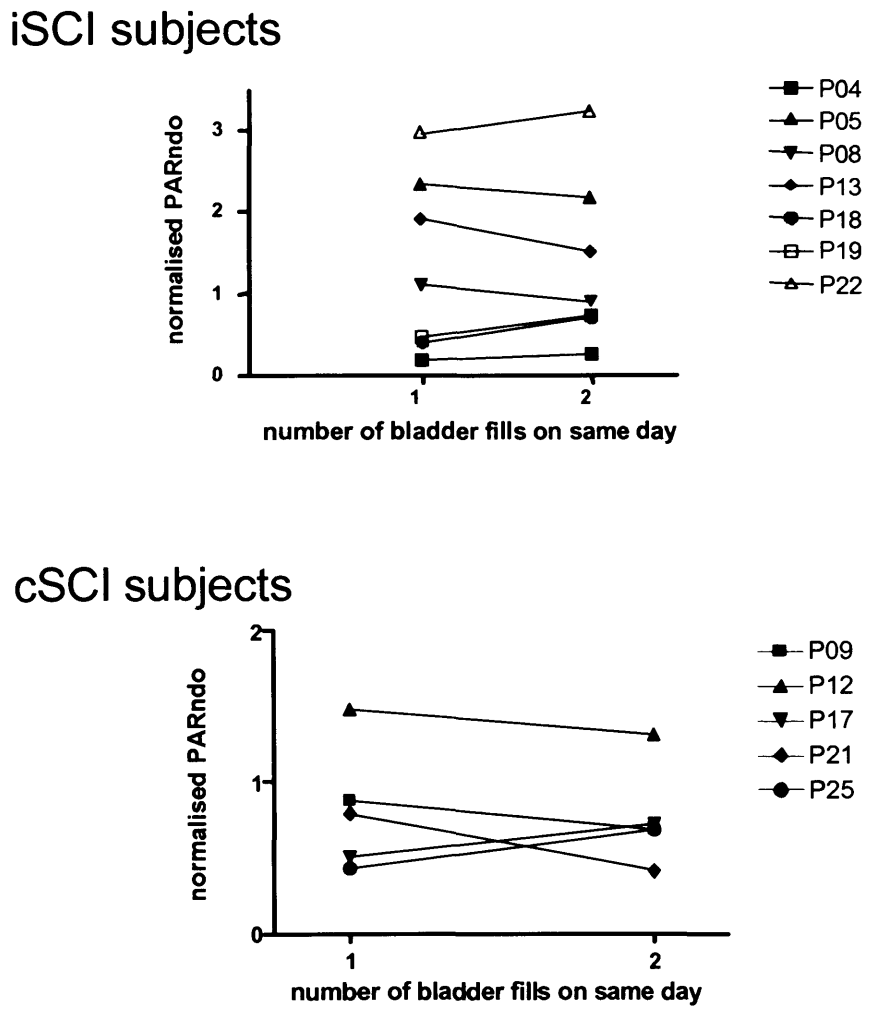


Figure 4.13 **$PAR_{void/ndo}$ Data Recorded From 2 Separate Bladder Fills During One Laboratory Visit In SCI Subjects**

High values for intra-class correlation (ICC) were obtained with statistical analysis indicating very good repeatability for this parameter

PARndo ICC = 0.98 (very good repeatability)

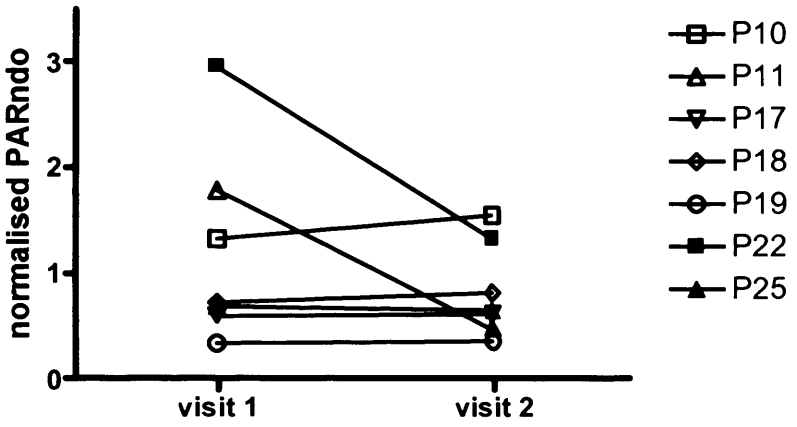


Figure 4.14 **$PAR_{void/NDO}$ Data Recorded For Two Separate Visits To The Laboratory In SCI Subjects**

Two measures for this parameter were taken on 2 separate visits to the laboratory by the subject.

Statistical analysis gave rise to an intra-class correlation of:
ICC for PARndo = 0.94 indicating very good repeatability for this parameter.

Discrepancies seen in subjects P11 and P22 were due to the PAR being elicited before periods of firing off (higher values) and post firing off (lower values). This highlighted the need to consider carefully at exactly what point the PAR was evoked to indicate the degree of voiding dysfunction.

Repeatability during a single visit

Figure 4.13 shows two PAR values recorded for two separate bladder fills during NDO on a single day. When the data from both iSCIs and cSCI subjects was pooled and statistically analysed very good repeatability was indicated by the high intra-class correlation PARndo ICC = 0.98. The PARndo parameter could be recorded in consecutive bladder fills with the confident expectation of consistent results.

Repeatability between separate visits

Subjects P10 (T1/T6 ASIA A), P11 (T1/T5 ASIA A), P17 (T1/T5 ASIA A) P18 (C8/C7 ASIA B), P19 (C7/C8 ASIA C), P22 (C5/T3 ASIA D) and P25 (T1/T4 ASIA A) were able to visit the laboratory more than once to test the repeatability of the kinesiological evoked PAR technique (figure 4.14). Statistical analysis of this data indicated that the PARndo parameter could be repeated fairly confidently in all these patients. The intra-class correlations for PARndo = 0.94 indicating very good repeatability.

4.4 Discussion

4.4.1 Suppression / Inhibition Of The Guarding Response

Normal micturition is preceded by relaxation of the EUS (Sundin and Petersen 1975; Vereecken and Verduyn 1970)- this and the detrusor contraction relies on the descending drive from the M-nucleus to the parasympathetic motorneurones in the sacral cord being turned "on" through the neurotransmitter glutamate (Blok et al, 1997). Relaxation of the sphincters relies on the descending excitatory drive from the M-nucleus activating sacral inhibitory interneurones in the intermediomedial cell column. The inhibitory neurotransmitters involved in this pathway are ≠-amino butyric acid and glycine, which inhibit sphincter motorneurones in Onuf's nucleus thereby suppressing the continuous excitatory activity from the L-nucleus, thus modulating the GR by switching it off -at the level of

the sacral cord- resulting in a suppression in EUS (and EAS) activity such that when the bladder contracts voiding can proceed unhindered and unobstructed.

Non-spinal subjects

During volitional voiding the PAR response (PARvoid) was attenuated (PARvoid < 1) indicating that the GR was suppressed sufficiently to allow unobstructed voiding. This correlation between suppression/inhibition of the sacral reflex activity and unobstructed voiding supports the findings of Dyro and Yalla (1986). Sethi et al (1989) found that only 90% of non-SCI subjects had no BCR during voiding, we found suppression of the PARvoid in 100% of our non-SCI subjects. This discrepancy may either be due to the greater sensitivity of our technique and/or the small sample size of our non-SCI population. Sethi et al (1989) found this suprasegmental ability to modulate the sacral reflex in a centrally integrated act resulting in the coordination of a detrusor contraction and simultaneous complete relaxation of the sphincter muscle essential for complete emptying is present even in the newborn period (age: 5 weeks).

In suprasacral spinal cord injuries the sacral and pontine micturition centres are separated such that reflex voiding is known to be initiated by involuntary detrusor contractions rather than relaxation of the EUS (Blaivas, 1982). If activation of the medial pontine nucleus was dysfunctional then the drive necessary for bladder emptying would also be missing.

Incomplete SCI subjects

Only a small fraction (21 %) of the iSCI subjects (cervical and thoracic) experienced severely obstructed voiding indicating the presence of DSD with small firing off/leak volumes and bladder end fill volumes. This type of clinical presentation might result from damage to the descending pathways

from the M-nucleus such that the excitatory drive from the L-nucleus on Onuf's nucleus is not switched off, resulting in tonic sphincter contraction.

Of the 2 subjects who experienced an inhibition of PAR activity during voiding, subject P07 was inhibited due to his surroundings. It has been shown (Blok 2002) in positron emission tomography (PET) scan studies that is it is the prefrontal cortex that is active when micturition takes place and during involuntary urine withholding. In an attempt to avoid this type of situation for the future an amendment to the protocol might be to set up a screen between the investigator and subject to increase the semblance of privacy for the subject, and to remove the catheter to further ease voiding. All subjects with good suppression/inhibition in PAR activity during NDO (PARndo < 1) had cervical lesions. These low PARndo values were accompanied by relatively large volumes being fired off (100 mL). Overall in this group of iSCI subjects normalised PARndo values were very variable ranging from near normal to grossly aberrant and found overall to be significantly higher than PARvoid in non-SCI subjects. The variability in the lesion was reflected in the large standard deviation in this group of iSCI subjects.

Complete SCI subjects

Increased PAR activity during voiding cystometry indicated a relative absence of inhibition/suppression of the GR. Concerning DSD, it was found that in general those subjects, whose urological reports indicated the presence of DSD, had significantly higher PARndo values than those who were without DSD. Only in 2 of these subjects did the volumes fired off during NDO reflect the presence of DSD being small and less that 80 mL. In one subject (P11) a high PARndo value is incongruently coupled with the large fired off volume indicates a deficit in the leaked/fired off volume collection system: It would be more efficient to devise an adjunct

collection system to collect the leaked/fired off volume for each PAR elicitation- instead of collecting the total volume leaked during a period of NDO through which several different PARndo values exist- as we have done here.

A mix of thoracic and cervical lesion subjects experienced a degree of suppression/inhibition in PAR activity during voiding cystometry, with corresponding high volumes being fired off. The average PARndo in this group of cSCI subjects was very similar to the PARefv of this group although significantly greater than PARvoid in the non-SCI subjects.

4.4.2 Detrusor Sphincter Dyssynergia

In spinally injured animals there is a suppression of the GR with the onset of bladder contraction (Barrington's 5^{th} reflex, 1928), which Barrington suggested was a sacral reflex. Clinical studies in cSCI humans show a high correlation between the loss of the GR and development of DSD, DSD being a phenomenon observed in man (monkeys and apes). This suggests (Siroky and Krane, 1982) the supraspinal control of the EUS, indicating that Barrington's 5^{th} is not a sacral reflex in man.

In this study PARndo > 1 was found to be a good indicator of DSD. DSD involves the involuntary phasic bladder contractions coupled with involuntary sphincter contractions (Sundin and Petersen, 1975). Barrington described the GR to come into play in response to urine in the urethra (Garry et al 1959). This flow of urine into the urethra may cause the activation of local stretch receptors leading to pudendal nerve-mediated bladder inhibition, initially suppressing bladder contractions because there is no supraspinal input the sphincter contraction is not sustained, so inhibition of the bladder contraction is not sustained either- so this dyssynergic cycle repeats. In contrast to the non-SCI subjects, some

subjects with supra-sacral lesions have an exaggerated pudendal reflex as expected during DSD (Dyro and Yalla, 1986; Sethi et al, 1989).

Siroky and Krane (1982) who using needle EMG of the external urethral sphincter found that of their SCI subjects, of those with no DSD, 95 % had preserved GR, the findings in this thesis showed that of those subjects with no DSD, only 30 % had preserved GR; Siroky and Krane (1982) showed that of those with DSD, 70 % had lost their GR, and the findings of this thesis showed that of those with DSD, 50 % had lost their GR. These percentage discrepancies in findings might be due to variations in methodology (CO_2 fills and CNE EMG) and sample size (Siroky and Krane, 1982, N=137). It was shown by Shahani (1970) that the electrophysiological profile of the bulbocavernosus reflex, and presumably other pelvic reflexes, approximate those of other human flexor reflexes, especially the blink reflex. It is well known that flexor reflexes develop an increased reactivity to cutaneous as well as visceral stimuli after spinal cord transection. Thus DSD may simply represent a simple flexor spasm in response to bladder distension or contraction in man. And Sethi et al. (1989) showed that in UMN SCI subjects suprasegmental inhibition of sacral reflexes is lost during voiding as demonstrated by EMG and is a more sensitive indicator of UMN lesions, but slightly less specific indicator than DSD- however we found a good correlation between the loss of inhibition (extent of PARndo>1) and the presence of DSD. The different types/classifications/grades of DSD were not investigated here because they have previously been shown (Weld et al 2000; Blaivas et al 1981) to have no correlation with the completeness or clinical neurological level of injury. Weld et al (2000) suggested that patients with cSCI and elevated intravesical pressures more often had DSD, however our data was more in agreement with those of Siroky and Krane (1982) who found that the

presence or absence of DSD correlated less well with completeness of spinal cord injury.

Dyro and Yalla (1986) demonstrated that with the silence of the EUS it becomes refractory in nature (lowered excitability) during voiding in non-SCI subjects, suggesting supraspinal involvement. They also demonstrated in subjects exhibiting DSD the sphincter does not become refractory, meaning that any stimulation, however small, during voiding would result in a contractile response sufficient to produce interruption of voiding.

In some of the SCI subjects no PAR was monitored during voiding cystometry even though their urological reports indicated the presence of NDO. There was variety of reasons for this: in some discomfort was experienced at which time the study was halted; or because normal void on urge was inhibited in the subject by the artificial laboratory surroundings; or the subject appeared to have a flaccid acontractile bladder, a loss in bladder compliance with no sensation or discomfort during bladder filling and no NDO; some subjects were taking medication or recreational drugs which are known to increase the compliance of the bladder. In light of this it is very important to take a very detailed history of the subject before experimentation. Clearly this would aid the interpretation of the results.

4.4.3 Repeatability

Unsurprisingly there was very poor repeatability between PAR values elicited during a single period of NDO. These values would be expected to differ according to whether the subject was firing off (leaking) and would be different according to how much the subject had fired off. As such, for future studies using this technique it is suggested a better collection

system devised so as to enable correlation between PARndo and the leak with which it was associated.

Good repeatability was found for PARndo measures for separate bladder fills on the same day and different days lending weight to the reliability of this technique to assess changes in GR if an intervention was given. Rodi and Vodusek (1995) found double pulse stimulation to be a reliable predictor of complete sacral reflex arc lesions, giving reproducible sacral reflex responses. The significant reproducibility of the data presented here supports their findings.

4.5 Conclusion

The clinical application of a positive sacral reflex during voiding lies in (Sethi et al., 1989) confirming an upper motorneurone type bladder dysfunction resulting from a lesion anywhere in the suprasacral neuroaxis in patients with urinary symptoms. The suppression/inhibition of the GR as measured using the modulation of PAR activity during voiding dysfunction could be an essential component of a neurophysiological tool to assess potential neural repair in those with SCI.

Chapter 5

Supra-Spinal Modulation Of The Guarding Response During Voluntary Effort

5.0 Introduction

Although most of the neural circuits involved in the normal control of the bladder are autonomic, continence is very much a function of volitional control. To re-cap, the guarding response (GR) is the progressive involuntary increase in sphincter activity that ensures continence as the bladder fills. When the sensory threshold of bladder fullness is reached this sphincter activity increases even further becoming a conscious and voluntary phenomenon as the person actively tries to remain dry in juxtaposition to a bladder wanting to empty (Park et al. 1997). Thus voluntary contraction of the pelvic floor muscles/the external urethral sphincter (EUS)/ the external anal sphincter (EAS) plays an important role in normal continence mechanisms particularly during postponement of voiding. That such contractions probably inhibit the parasympathetic reflex pathways within the spinal cord to suppress premature voiding contractions makes the quantitative assessment of this volitional control of interest.

Clinical examination of the sacral dermatomes and sacral reflexes (pudendo-urethral (PUR) and pudendo-anal reflexes (PAR)) and testing of voluntary contraction of the EAS are of primary importance to assess the integrity of the sacral segments. In complete supra-sacral spinal cord injury (ASIA grade A) the expectation would be a total loss of all volitional effects and sensations related to pelvic function. In people with incomplete lesions (ASIA grades B-D) the expectation would be much more variable with some preservation of voluntary modulation of their pelvic floor and sphincter reflexes including the GR.

5.1 Aim

The aim of this study was to investigate whether the modulation of the PAR by volitional effort is the same in non-SCI and SCI subjects; and whether the sensitivity of the more traditional method of integrated EMG is the same as analysing the evoked-PAR in assessing voluntary effort.

5.2 Methods

Subjects were presented with an audio signal instructing them to make a voluntary squeeze of their anal sphincter (imagine or attempt to do so in the case of those with SCI classified as ASIA A) and hold it for the duration of the signal (the paired pulse). During the attempted contraction, the computer controlling the experiment elicited a PAR response (figure 5.0). The test was repeated ten times and the electromyogram was integrated automatically to determine the averaged evoked pudendal-anal reflexes (PARvc), and the peak to peak amplitude of the PAR response measured (right branch in figure 5.1). From the raw electromyogram, the more traditional integrated electromyograms (iEMG) were determined for each subject during voluntary contraction of the pelvic floor and at rest (figure 5.1- left branch).

Statistical Analysis

All PAR values were standardised to PAR when the pelvic floor of the subject was relaxed. All data was pooled and expressed as a mean (±SD). Clinical statistical significance between SCI and non-SCI subject data was determined with 95% confidence interval using an unpaired 2-tailed t-test with Welch's correction. [The unpaired t test assumes that the two populations have the same variances. Since the variance equals the standard deviation squared, this means that the populations have the same standard deviation). A modification of the t test (developed by Welch) is used when one is unwilling to make that assumption].

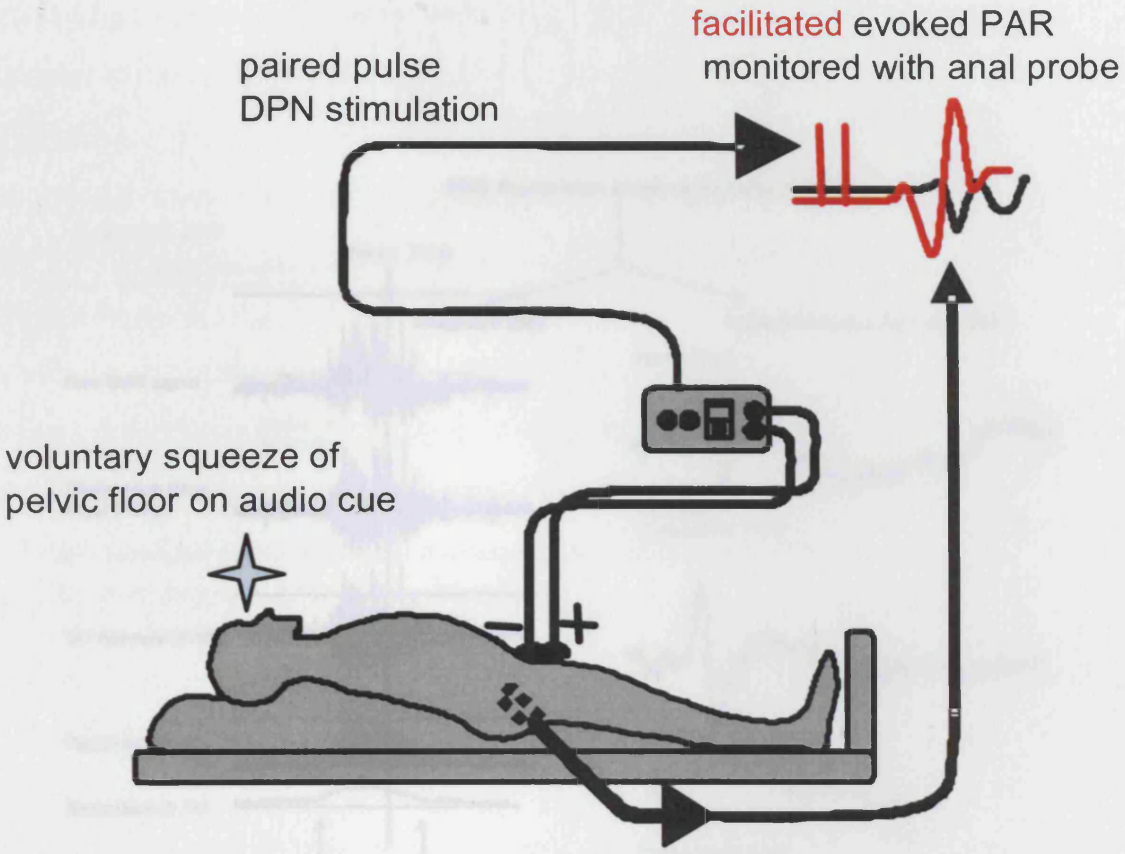


Figure 5.0 **Set Up For Modulation Of The Bladder Guarding Response During Voluntary Effort**

The experimental arrangement of the subject is shown with the dorsal penile nerve stimulation (DPN) with its facilitated evoked pudendo-anal reflex (PAR) response, in red. The response is facilitated in response to the voluntary squeeze of the pelvic floor that is monitored with the anal probe.

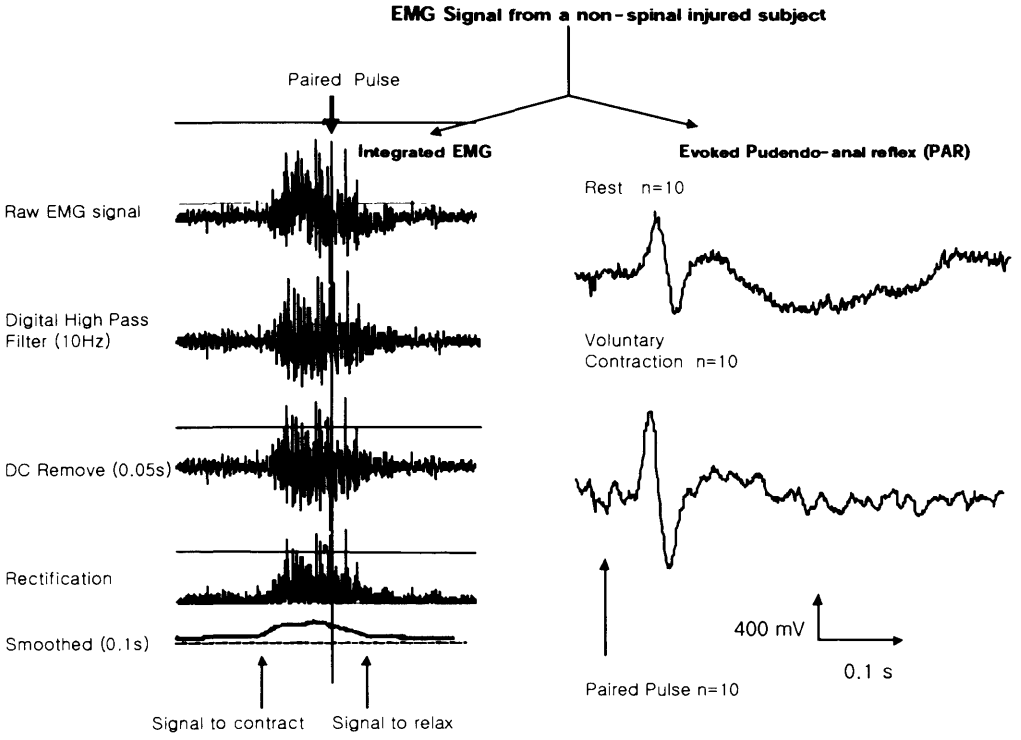
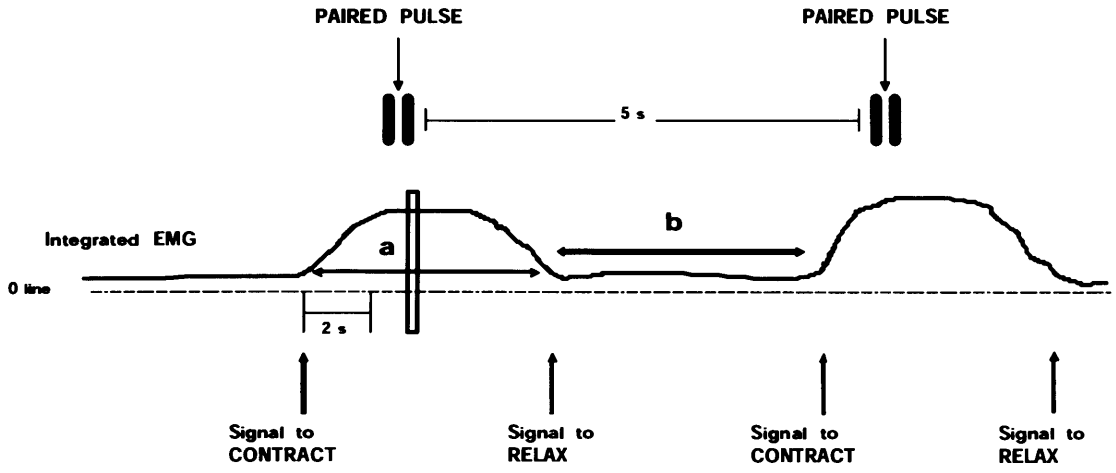


Figure 5.1 Processing Of The 2 Different Neurophysiological Measures For The Assessment Of Volitional Effort For Pelvic Floor And Sphincter Contraction

During voluntary contractions of the pelvic floor muscles and sphincters (squeeze) the evoked pudendo-anal reflex (PAR) is facilitated and measured by its peak to peak amplitude (the right branch). The raw EMG integration processing paradigm employed is shown on the left branch.



50 ms period excluded to remove the effect of the paired pulses to the dorsal penile nerves

a mean value taken during attempt of or voluntary contraction of the pelvic floor

b mean value taken during relaxation of pelvic floor

Figure 5.2 **Paradigm To Process The Integrated EMG Signal**

The above shows an integrated (smoothed) EMG signal profile containing 2 pelvic floor contractions which were started just before a paired pulse DPN signal such that the evoked PAR would have the full effect of the contraction. The vertical arrows show the signal to begin and end such a contraction. The horizontal arrows for 'a' and 'b' constitute equal time periods for which a mean EMG signal activity was recorded, averaged for 10 paired pulses and substituted into the % change in response equation found in the text. In the case of recordings for 'a', at least 50 ms was excluded (shaded bar) so that stimulus artefact resulting from the DPN stimulation did not contaminate the data.

5.3 Results

5.3.1 Analysis Of The Pudendo -Anal Reflex Response

The analytical technique that has been adopted for the analysis of the PAR response is the same as that described in chapter 3 that is based on normalisation. In the equation presented in diagram 3.1 (in chapter 3), baseline condition, C_0 was the peak to peak amplitude of the PAR tested when the pelvic floor of the subject was relaxed and test condition, C_T was the peak to peak amplitude of the PAR tested during a voluntary pelvic floor squeeze/contraction in non-SCI and iSCI subjects or during an imagined contraction in iSCI and cSCI subjects. The normalised value was termed the voluntary contraction factor, PARvc, (figure 5.1-right branch).

5.3.2 The Sensitivity Of The Evoked Pudendo -Anal Reflex Response With Volitional Effort

To assess the accuracy and sensitivity of the use of the evoked PAR response as a method of assessing residual volitional ability, the percentage change in response was calculated for the PAR response and for the integrated EMG response with volitional effort and compared to one another.

The degree of percentage change in response due to voluntary contraction was calculated as the difference of the average (n=10) of the response values with and without voluntary contraction of the pelvic floor, divided by the average without voluntary contraction (i.e. PAR or iEMG when the pelvic floor was relaxed):

$$\text{percentage change in response (R)} = [(R_{VC} - R_{resting}) / R_{resting}] \times 100$$

as determined for each variable where R was the averaged PAR or the integrated EMG response.

For the PAR response with volitional effort (in reference to diagram 3.1):

$$\% \text{ change in PAR response} = \frac{[C_T - C_0]}{C_0} \times 100$$

5.3.3 Traditional Integrated EMG Analysis

An example of the processing of the traditional method of integrated EMG analysis is shown, starting in the left branch of figure 5.1 which then follows into figure 5.2. This paradigm in illustrates the sampling employed for 1 paired pulse. This was repeated for ten controls (no contraction 'b') and ten tests (with contraction 'a') in each subject. The means of 'a' and 'b' were then substituted into the equation above (Rvc and Rresting respectively).

The Effect Of Pelvic Floor Contraction On The Pudendo-Anal Response Latency

Facilitation of the PAR response with voluntary contraction of the pelvic floor was shown by a statistically significant shortening in the average of latency in all 3 groups (Figure 5.3).

The Effect Of Pelvic Floor Contraction On The Pudendo-Anal Response

A comparison of these 2 techniques of assessing volitional ability is graphically presented in figure 5.4. The traditional established method: percentage change in iEMG (hatched bars) was able to differentiate the cSCI subjects from the other subject groups ($p< 0.05$).

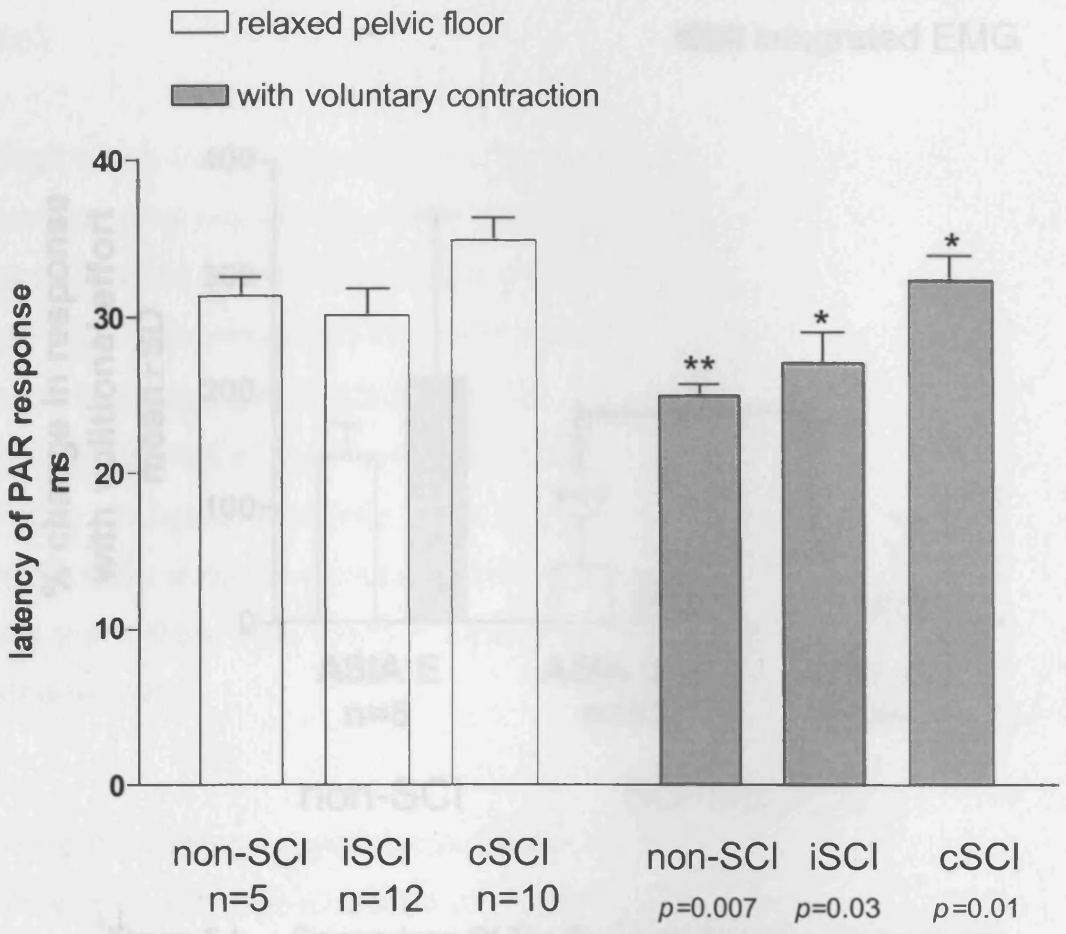


Figure 5.3 The Effect Of Pelvic Floor Contraction On The Latency Of The Pudendo-Anal Reflex Response

The latency of the PAR response was significantly shortened with the voluntary contraction of the pelvic floor in all 3 cohorts. The open bars indicate the mean±stdev latency in the 3 groups recorded when the pelvic floor is relaxed and the hatched bars indicate the latency when the pelvic floor is contracted. Comparisons were made between the relaxed state and the contracted state latencies with paired t-tests. Significance is indicated with *p* values and summaries: non-SCI mean of differences 6.3, 95% confidence interval 2.8 to 9.8; iSCI mean of differences 3.1, 95% confidence interval 0.3 to 5.9; cSCI mean of differences 2.5, 95% confidence interval 0.5 to 4.5.

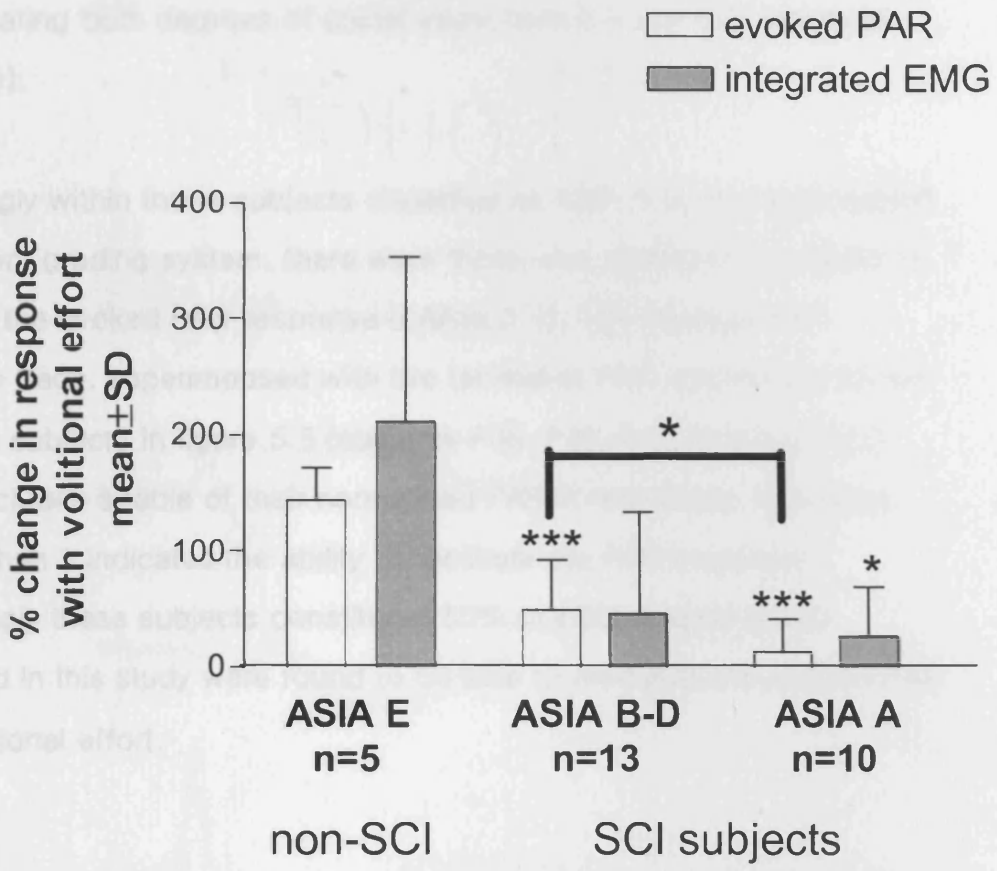


Figure 5.4 Comparison Of The Percentage Change In Response Detected By The 2 Neurophysiological Measures During Voluntary Pelvic Floor Squeeze.

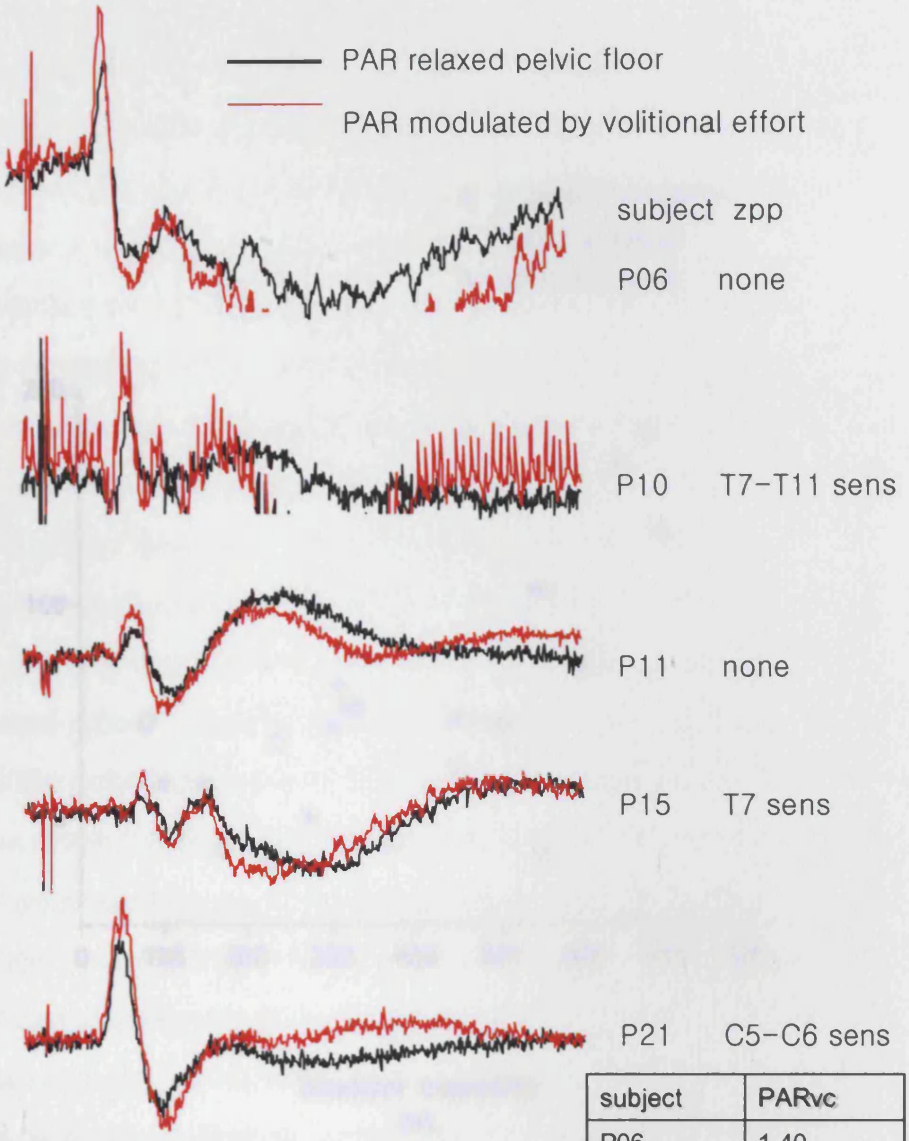
Measure 1 Evoked PAR: clear bars
Statistical significance *** denotes p <0.0001 indicating that percentage change in PARvc for both incomplete and complete SCI subjects are significantly different to non-spinal subjects;
* denotes p <0.05 significant difference between incomplete and complete SCI subjects

Measure 2 Integrated EMG: hatched bars
Statistical significance * denotes p <0.05 indicating that only those SCI subjects graded as ASIA A are significantly different to non-spinal injured subjects

However the averaged evoked PAR technique differentiated between the iSCI subjects (p <0.05) and the cSCI subjects (clear bars), as well as differentiating both degrees of spinal injury from the non-SCI subjects (p<0.0001).

Surprisingly within those subjects classified as ASIA A by the ASIA/IMSOP Impairment grading system, there were those who displayed the ability to facilitate the evoked PAR response (PARvc > 1). The average PAR response trace, superimposed with the facilitated PAR response is shown for these subjects in figure 5.5 (subjects P06, P10, P11, P15 and P21) which includes a table of their normalised PARvc responses. Any value greater than 1 indicates the ability to facilitate the PAR response. Surprisingly these subjects constituted 50% of cSCI subject group assessed in this study were found to be able to modulate the evoked PAR with volitional effort.

Considering the volitional aspect involved in continence, analysis of the bladder capacity with the percentage change in PAR response with pelvic floor contraction was assessed – results are shown in figure 5.6. The Spearman correlation coefficient indicates that a highly significant (p = 0.0002) and positive (rs 0.6) relationship exists between these two parameters.



subject	PARvc
P06	1.40
P10	2.00
P11	1.64
P15	1.48
P21	1.38

Figure 5.5 Facilitation Of The Evoked Pudendo-Anal Reflex Response In Subjects Classified As Complete SCI Subjects As Per The ASIA/IMSOP Impairment Scale

The dashed line traces show the PAR for subjects when their pelvic floor was relaxed. The superimposed solid line trace is the average evoked PAR when the subject was asked to contract their pelvic floor. These 5 subjects were graded ASIA A as assessed using the ASIA/IMSOP impairment scale, but unexpectedly are seen here to be able to facilitate the PAR suggesting the presence of residual cerebro-spinal motor pathways which remained undetected by the gold standard ASIA/IMSOP Impairment Scale.

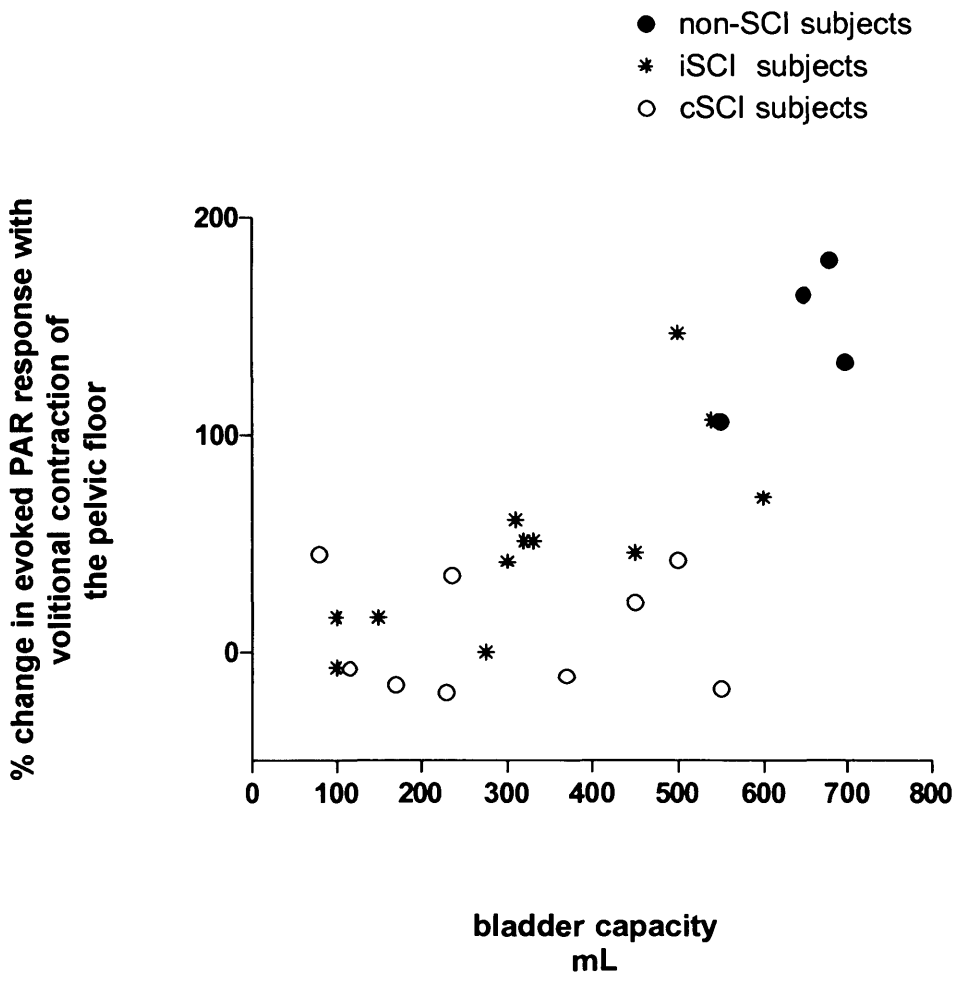


Figure 5.6 **Correlation Of Percentage Change In Pudendo-Anal Reflex Response With Bladder Capacity**

The Spearman correlation coefficient, rs = 0.6 (95% confidence interval of 0.3 to 0.8) indicated a highly significant (p = 0.0002) positive relationship between the ability of an individual to facilitate their PAR response and their bladder capacity.

5.4 Discussion

Although most of the neural circuits involved in the normal control of the bladder are autonomic, continence is very much a function of volitional control. Voluntary contraction of the pelvic floor muscles plays an important role in normal continence mechanisms particularly during postponement of voiding. When the bladder achieves its near-maximal capacity at end fill volume, not only does contraction of the sphincters prevent inadvertent leaking but such contractions probably inhibit the parasympathetic reflex pathways within the spinal cord to suppress premature voiding contractions. This mechanism could operate directly via descending cortico-spinal pathways leading to inhibition of sacrally mediated visceral reflexes. Indirectly there could be facilitation of the motor component of the guarding response that in turn activates pudendal afferents to suppress the visceral reflexes. Such a mechanism would be similar to that envisaged for electrical neuromodulation (Craggs and McFarlane, 1999). Hence, the sensations of a full bladder and the strong desire to void can also be suppressed by voluntary contractions of the pelvic floor, or again, by therapeutic neuromodulation (Oliver et al, 2003). It remains to be determined whether people with an incomplete spinal cord injury and some volitional control over their pelvic floor can also voluntarily inhibit their detrusor hyperreflexia and suppress the desire to void.

Measuring the effects of volition on the pelvic sphincters in some cord-injured people, for example those with a putative complete injury (as determined by the ASIA classification), is difficult. The normal PAR response was easily facilitated by voluntary contractions of the pelvic floor in non-SCI subjects. In people with incomplete lesions (ASIA B-D) it was found that there was some preservation of voluntary modulation of their pelvic floor and sphincter reflexes. Surprisingly 50% of the complete supra-sacral spinal cord injury (ASIA A) subjects had preserved volitional

effects related to pelvic function demonstrable in the ability to facilitate the PAR response. There maybe two possible inter-related explanations for this finding- or a combination of both.

5.4.1 Discomplete SCI subjects

In the first instance it maybe that the volitional ability in the subjects indicated the presence of remaining cortico-spino-bulbo pathways which had remained undiscovered and untapped so far as putative rehabilitation was concerned. Researchers have used the term *discomplete* to encompass a syndrome of neurophysiological findings to differentiate SCI subjects who, although clinically paralyzed, showed such subclinical evidence of translesional motor connections. Also histological studies of Kakulas,(1988) showed in post-mortem material in the hyper acute situation that many of the so-called clinically complete cases were, in fact, significantly incomplete.The term `discomplete' was first introduced by Dimitrijevic et al (1983; 1988) to explain their finding of electrophysiological transmission of signals across the lesion in patients who were clinically complete having lost all sensation and voluntary motor functions below the level of the lesion.

5.4.2 Autogenics

The second explanation could be that this finding could result from the science of autogenics. In this study, to assess volitional ability in the cSCI subjects, the subjects were asked to visualise contracting their sphincters/pelvic floor. Visualization and imagery (autogenics) and the effects that can potentially result from engaging in such activity are not a new concept. Autogenic studies have proven visualization to affect many body systems (Blumenstein et al 1995; Rider et al 1985; Izumi et al. 1995; and Ikai et al 1996). Izumi et al. (1995) generated an interesting study in 1995-titled "Facilitatory effect of thinking about movement on motor

evoked potentials to transcranial magnetic stimulation of the brain." The results clearly displayed that the median MEP values during only thinking about thumb abduction was twice that at rest (p=0.008) and one half that during voluntary contraction (p=0.008). Their further research provided scientific evidence supporting that a relationship exists between autogenic training and muscle response. It is hypothesized that facilitation by voluntary contraction may occur at both a spinal and a cortical level. Furthermore it is thought that merely thinking about movement may cause facilitation at the spinal cord level since corticospinal descending volleys may also increase (Ikai et al 1996).

5.4.3 New versus old Assessment techniques

It was found that the more traditional integrated electromyogram assessment technique was able to discern only the complete spinal injured subjects from the other subject groups. However the evoked PAR response technique distinguished the iSCI subjects from the cSCI subjects. This indicated its greater sensitivity for the completeness of a lesion. For convenience, the PAR response technique has proved to be one of the easiest and most useful sacral somatic reflexes to test.

5.5 Conclusion

It has been shown that in patients with a mixture of stress and urge urinary incontinence suggests that pelvic floor exercises can be very therapeutic and durable (Nygaard et al 1996). It may be that cerebro-spinal activation, through residual voluntary contractions can produce a durable and therapeutic restoration of normal function of the guarding reflex in people with an incomplete spinal cord lesion. And for those subjects classified as ASIA A this technique of assessment of residual motor control traversing a spinal cord lesion may allow the early identification of preserved volitional

control which if trained and supported, could become useful movement over time.

Chapter 6

Modulation Of The Bladder Guarding Response By Transcranial Magnetic Stimulation

6.0 Introduction

The potential for utilising preserved voluntary pathways in SCI may well help to restore normal function by facilitating sacral reflexes such as the pudendo-anal reflex response. The importance of cortical influences in the control of the external anal sphincter (EAS) is well recognised. In higher cortical areas, transcranial magnetic stimulation (TMS) can be used to tease apart specialized processing mechanisms. TMS is rapidly developing as a powerful, non-invasive tool for studying the human brain. Stimulation of the motor areas of the human brain through the intact scalp with a pulsed magnetic field creates current flow in the brain and can temporarily excite or inhibit specific areas. This activation of the motor cortex produces a relatively synchronous muscle response, the motor evoked potential (MEP) in the target muscle. TMS of the motor cortex has been used as a means of evaluating the extent of spinal cord injury (Ackermann et al. 1992) and to monitor the recovery of skeletomotor function during rehabilitation after injury (Clarke et al. 1994; Davey et al. 1998; Puri et al. 1998; McKay et al 2004; Norton and Gorassini, 2006). In pelvic dysfunction research TMS of the motor cortex has been used to non-invasively study the integrity of the descending tracts to the EAS by recording the evoked EMG or manometric responses (Opsomer *et al.*, 1989; Loening-Baucke *et al.*, 1994; Turnbull *et al.*, 1994). The application of conditioning TMS to nerves innervating pelvic musculature using the St. Mark's electrode has been shown to modulate cortical pathways to the EAS (Hamdy *et al.* 1998). However it is know that the St. Mark's electrode stimulates both pudendal afferent and efferent nerves. The mechanism of modulation by TMS may

be more sensitively ascertained using pudendal afferent stimulation by DPN stimulation to investigate cortical influences on the EAS.

6.1 Aim

The aim of this preliminary study was to investigate the relationship between the activation of cortico-spinal pathways using transcranial magnetic stimulation (TMS) and the PAR comparing people with and without incomplete spinal cord injuries.

6.2 Methods

Contraindications of use of MAGSTIM stimulator

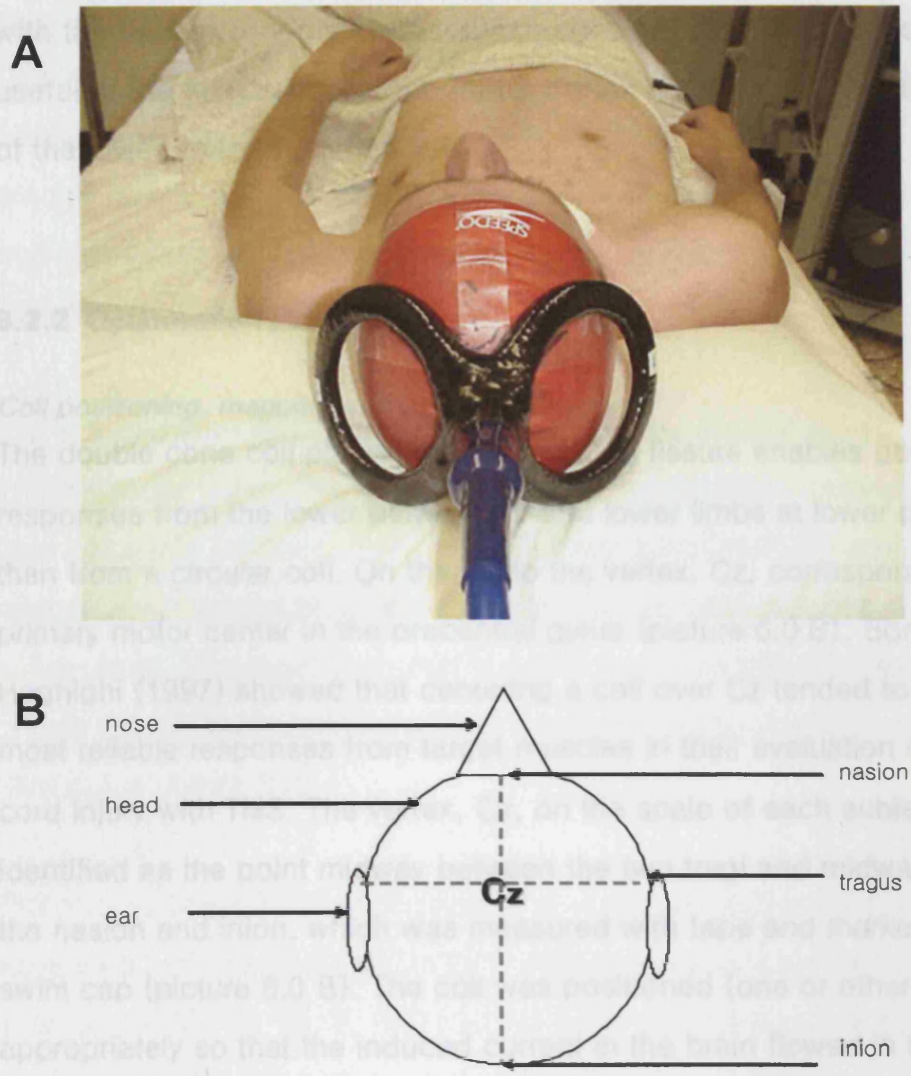
The MAGSTIM 200 was not used on or in the vicinity of patients or users with cardiac demand pacemakers, implanted defibrillators and/or implanted neurostimulators.

6.2.1 Experimental Set-Up

Electromagnetic stimulation of the brain was achieved using a 2 Tesla MAGSTIM 200 stimulator (MAGSTIM) connected to a double cone coil centered over the vertex of the subjects head which was covered by a close fitting swim cap with a chin-strap (picture 6.0 A).

Magnetic coil

The 110mm double cone coil (Type 9902-00 MAGSTIM, picture 6.0 A) has 2 large, curved-shaped windings positioned side by side with a flat central section, its angled sides closely fitting the subject's head. The advantage of this coil is that its geometry allows for better magnetic coupling, giving significantly higher induced current in the central fissure (70% higher than



Picture 6.0 Double Cone Coil Placement

A Electromagnetic stimulation of the brain was achieved using a 2 Tesla Magstim 200 stimulator (MAGSTIM) connected to a double cone coil centered over the vertex (Cz) of the subjects head which was covered by a close fitting swim cap with a chin-strap shown here with an iSCI subject.

B Overhead view of subjects head: the vertical dashed line measures from the nasion (bridge of the nose) to the inion (indent of skull) -the halfway point of this line is marked on the scalp/cap; the horizontal dashed line between each tragus (just in front of each ear) -the halfway point of this line is marked on the scalp

with the usually recommended 90mm circular coil). This coil is especially useful in the stimulation of the motor cortex areas controlling the muscles of the lower torso and limbs.

6.2.2 Optimisation Procedure

Coil positioning, mapping and localisation

The double cone coil placed over the central fissure enables good responses from the lower pelvic floor and lower limbs at lower power levels than from a circular coil. On the scalp the vertex, Cz, corresponds to the primary motor center in the precentral gyrus (picture 6.0 B). Bondurant and Haghighi (1997) showed that centering a coil over Cz tended to evoke the most reliable responses from target muscles in their evaluation of spinal cord injury with TMS. The vertex, Cz, on the scalp of each subject was identified as the point midway between the two tragi and midway between the nasion and inion, which was measured with tape and marked on the swim cap (picture 6.0 B). The coil was positioned (one or other side up) appropriately so that the induced current in the brain flowed in the required direction to activate the pudendo-anal reflex.

The reliability of the coil position was further confirmed by asking the non-SCI subject to flex his toes such that his toes were seen to 'jerk' in response to a single TMS pulse. It has been previously confirmed in other studies that this facilitation manoeuvre improves the recording of muscle responses in subjects with incomplete injuries (Bondurant and Haghighi, 1997; Thompson et al., 1987).

TMS optimization

This study included 3 non-SCI subjects and 3 incomplete SCI subjects. Subjects' lay supine on their back with feet flexed (if they were able), with the coil held over the vertex (picture 6A). Stimulus intensity started at 35% and was increased to the maximum most tolerable level, which caused dorsiflexion (the flexed toes 'jerk').

6.2.3 Stimulation Protocol For Magnetic And Electrical Pulses

The magnetic pulse moved across the DPN stimulation, separated by a time interval, z (milliseconds), being initially advanced (-z) and then retarded (+z) in relation to the DPN stimulation. DPN stimulation was kept supra-motor threshold such that the PAR response elicited was seen clearly for any facilitation or inhibition effects by the interaction with the TMS pulse (figure 6.0).

Protocol optimisation was conducted on one non-SCI subject only. Initially advanced (-z) maximal TMS to DPN stimulation was used at intervals: 100ms, 50, 20, 15, 10, 8, 5, 0 ms. However considering that the minimum reaction time for a voluntary contraction is between 200ms to 400ms indicating that an interval of 200ms encompasses the activating of voluntary modulatory pathways which might inhibit the effect of DPN stimulation, time intervals, z were altered to: 0.2, ±5, ±10, ±20, ±40, ±80, ±160, ±320 ms with DPN-evoked PAR control responses recorded between each combined stimulation. This protocol was then repeated in the other subjects.

6.2.4 Analysis of motor responses to combined TMS and DPN stimulation

Cambridge Electronic Design signal averaging software (CED plus Spike 2) generated the averaged rectified PAR response from which the peak to peak

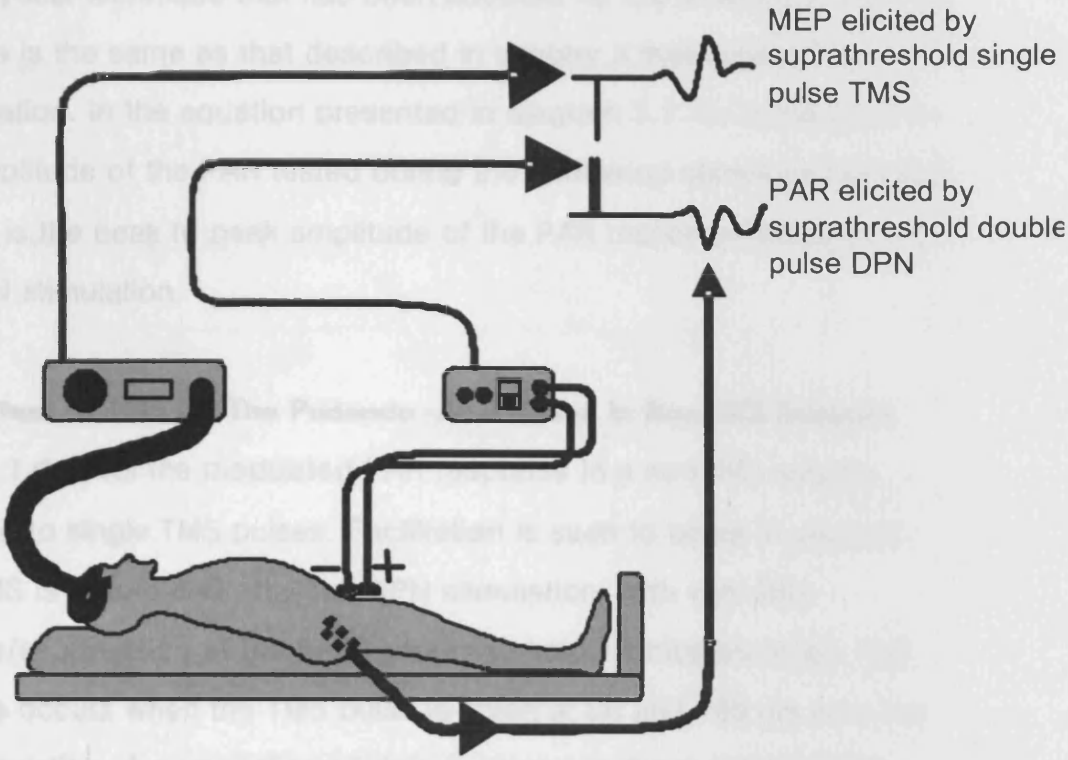


Figure 6.0 Set Up

The experimental arrangement of subject, the transcranial magnetic stimulation (TMS) and dorsal penile nerve stimulation (DPNS) with their respective evoked responses, the motor evoked potential (MEP) of the anal sphincter and pudeno-anal reflex (PAR).

amplitude of the PAR response was measured with the muscles relaxes and during periods of maximum voluntary contraction.

6.3 Results

Analysis Of The Pudendo-Anal Reflex Response

The analytical technique that has been adopted for the analysis of the PAR response is the same as that described in chapter 3 that is based on normalisation. In the equation presented in diagram 3.1: C_T is the peak to peak amplitude of the PAR tested during the combined stimuli of TMS and DPN; C_0 is the peak to peak amplitude of the PAR response tested during only DPN stimulation.

6.3.1 Effect Of TMS On The Pudendo-Anal Reflex In Non-SCI Subjects

Figure 6.1 depicts the modulated PAR response in a non-SCI subject subjected to single TMS pulses. Facilitation is seen to occur in general when TMS is before and after the DPN stimulation, with very little inhibition/suppression of the PAR response. Actual inhibition of the PAR response occurs when the TMS pulse is given at 80 and 160 ms post the DPN stimulation. A compilation of data is shown in figure 6.2 for the 3 non-SCI subjects to expose the variability in the PAR response to time-domain variation of the TMS pulse.

Facilitation Of The Pudendo-Anal Reflex Response By TMS In Non-SCI Subjects

In the non-SCI subjects shown in figure 6.2, the effect of TMS on the PAR is shown on the same time scale and the points of greatest facilitation of the PAR in subject 1WS occurred when the TMS was given -5 to 5ms pre and post the DPN paired pulse; in the 2nd non-SCI subject 2MDC greatest

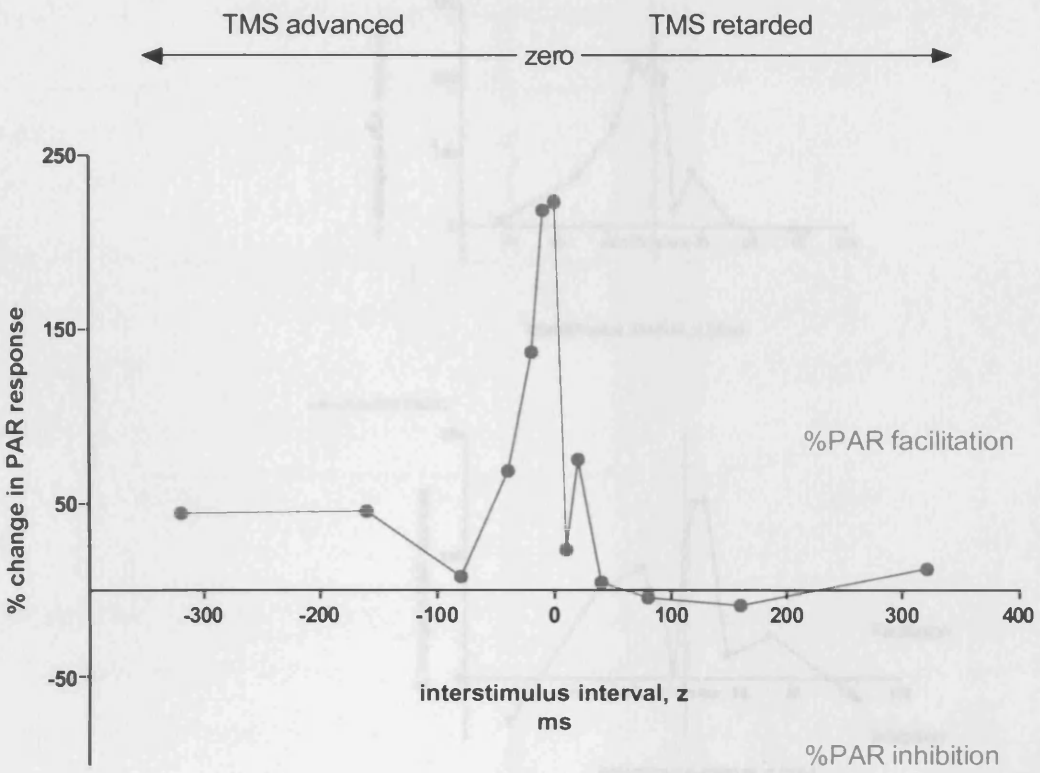


Figure 6.1 Example Of The Modulation Of The Pudendo-Anal Reflex Response With TMS In A Non-SCI Subject

Y-axis values show the percentage change in PAR response. X-axis values show the interval, z in milliseconds between the paired DPN stimulation and single TMS pulse. Negative z intervals indicate that the TMS pulse was given in advance of the DPN pulse; and positive z intervals indicate that the TMS pulse was given post-DPN stimulation. Above the x-axis are facilitatory effects on the PAR response, and below it are inhibitory.

Greatest facilitation of the PAR response occurs at or around synchronization of the stimulations in this subject.

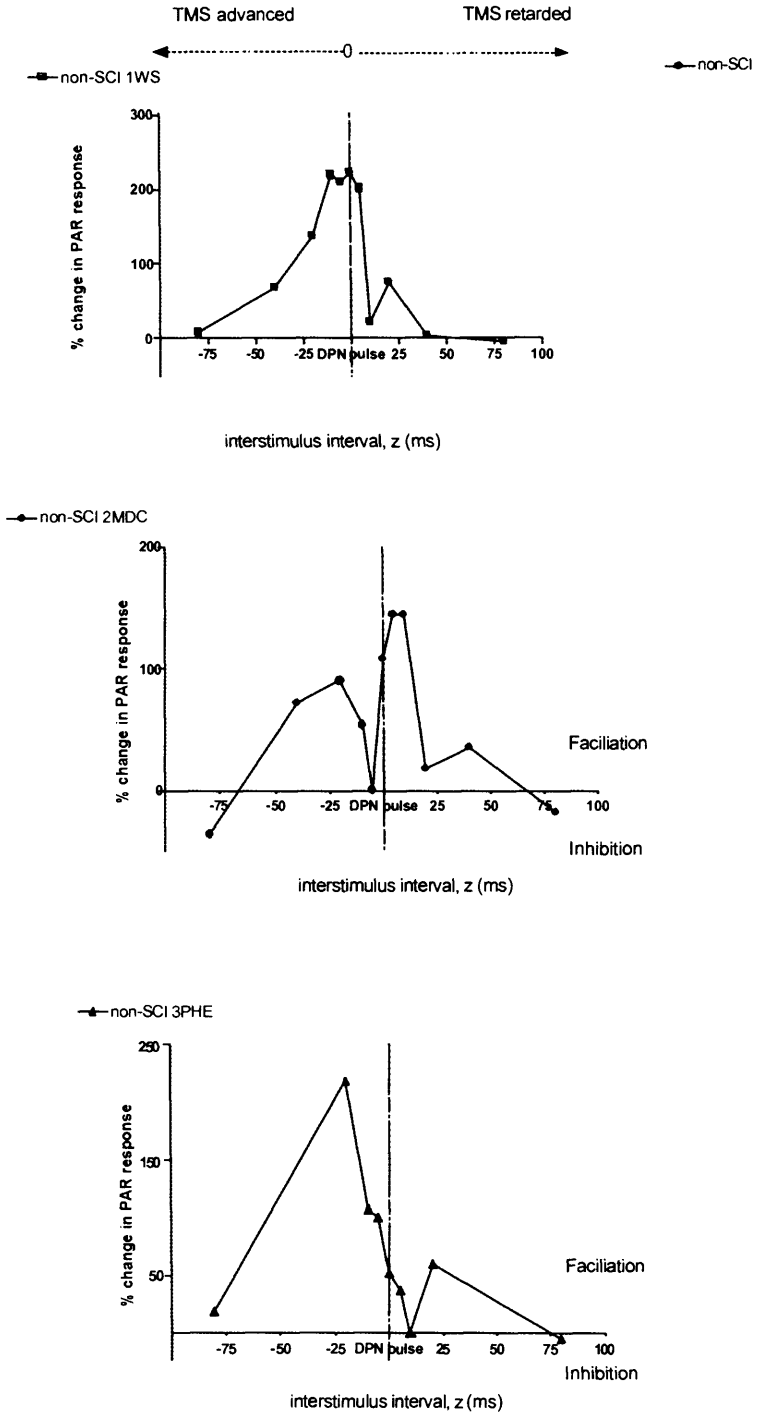


Figure 6.2 **Modulation Of The Pudendo-Anal Reflex Response In Non-SCI Subjects**

In all cases y-axis values show the percentage change in PAR response, above the x-axis are facilitation of the PAR response, and below it are inhibition.

Variation exists between these 3 subjects although in broad terms the greatest facilitation occurs at or around synchronisation

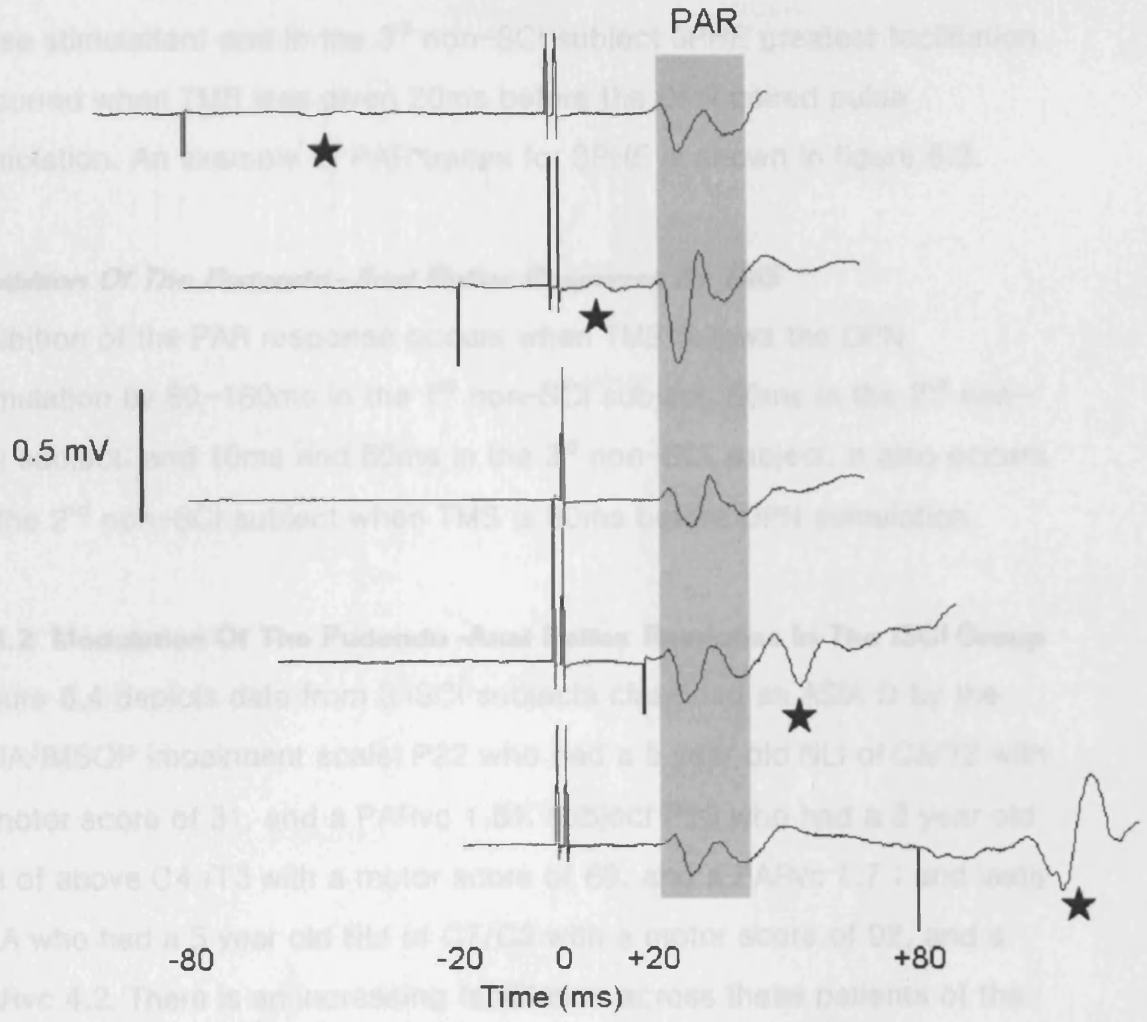


Figure 6.3 Example Of Modulation Of Pudendo-Anal Reflex Response With TMS In A Non-SCI Subject

Conditioning interval from TMS at -80 ms to TMS at +80 ms relative to the DPN stimulation at time zero. The PAR is highlighted by a vertical grey box. Any response to TMS is marked with a star. Note the maximal facilitation of the PAR at -20 ms to 0ms conditioning interval in a non-SCI subject. Interestingly, in this subject, when the PAR became the conditioning stimulus there was sometimes a significant facilitation of the TMS at +20 and +80 ms.

facilitation occurred when TMS was given 5 and 10ms after the DPN paired pulse stimulation; and in the 3rd non-SCI subject 3PHE greatest facilitation occurred when TMS was given 20ms before the DPN paired pulse stimulation. An example of PAR traces for 3PHE is shown in figure 6.3.

Inhibition Of The Pudendo-Anal Reflex Response By TMS

Inhibition of the PAR response occurs when TMS follows the DPN stimulation by 80-160ms in the 1st non-SCI subject; 80ms in the 2nd non-SCI subject; and 10ms and 80ms in the 3rd non-SCI subject. It also occurs in the 2nd non-SCI subject when TMS is 80ms before DPN stimulation.

6.3.2 Modulation Of The Pudendo-Anal Reflex Response In The iSCI Group

Figure 6.4 depicts data from 3 iSCI subjects classified as ASIA D by the ASIA/IMSOP Impairment scale: P22 who had a 5 year old NLI of C5/T3 with a motor score of 31, and a PARvc 1.61; subject P26 who had a 3 year old NLI of above C4 /T3 with a motor score of 89, and a PARvc 1.7 ; and lastly PAA who had a 5 year old NLI of C7/C3 with a motor score of 92, and a PARvc 4.2. There is an increasing facilitation across these patients of the PAR as one descends down the page as the subjects have increasing motor scores - this is also supported by their normalised PAR response when facilitated with voluntary contraction of the pelvic floor and sphincter.

TMS before DPN stimulation

In subject P22, when TMS was in advance of the PAR response, in the majority, facilitation was seen, with inhibition of the PAR response only at -10 ms, -80 ms and -320 ms. In subject P26, again facilitation was prevalent, with only a very small inhibition at -80 ms. In subject PAA no

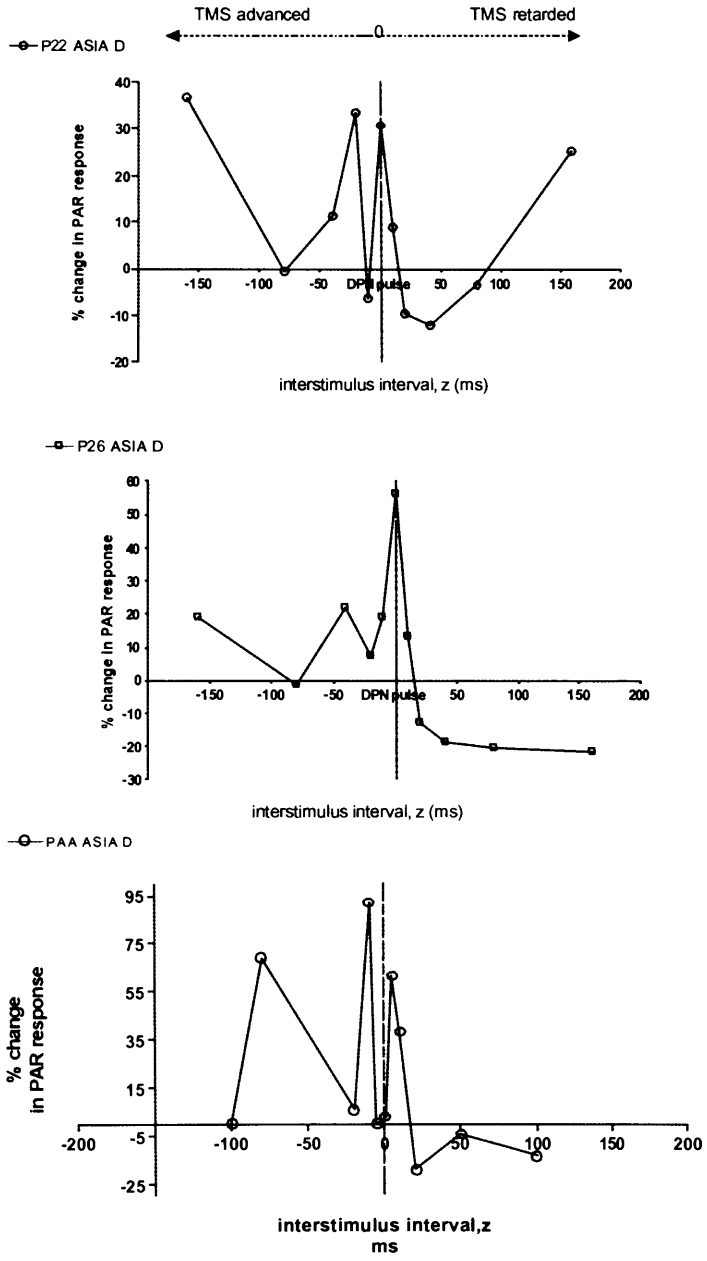


Figure 6.4 **Modulation Of The Pudendo-Anal Reflex Response With TMS In Incomplete SCI Subjects**

Y-axis values show the percentage change in PAR response, above the x axis are facilitation of the PAR response, and below it are inhibition.

Great variability exists between the subjects. In descending order they have increasing amounts of PAR facilitation by the TMS pulse.

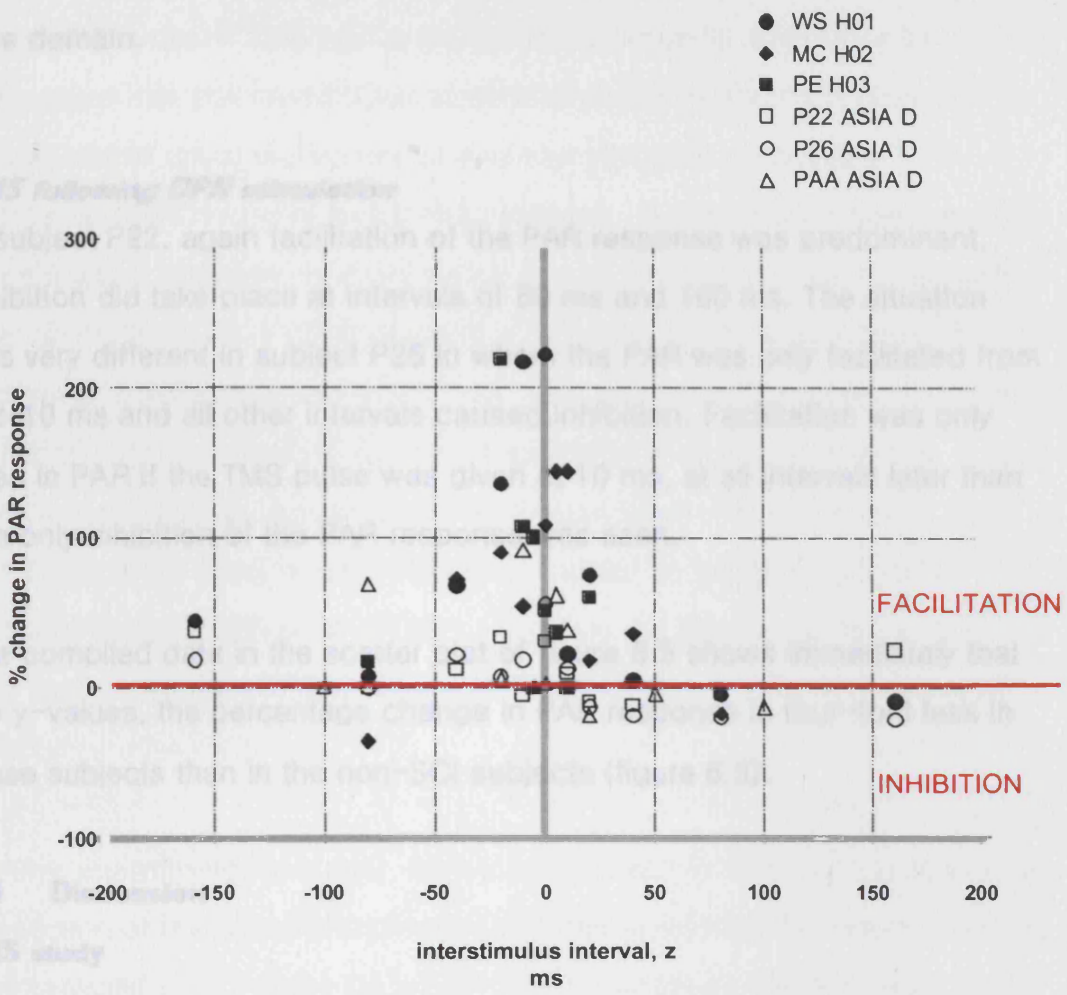


Figure 6.5 Scatter Plot Of Modulated Pudendo-Anal Reflex Response By TMS

Open symbols indicate the iSCI subjects and filled symbols indicate non-SCI subjects. Greater variance between the 2 subject groups exists at or around synchronous application of DPN and TMS. Above the red line are facilitated PAR responses; below the red line are inhibited/suppressed PAR responses. Zero on the x-axis indicates the point at which the TMS pulse and paired pulse DPN stimuli coincide.

inhibition of the PAR response was seen when TMS was in the advanced time domain.

TMS following DPN stimulation

In subject P22, again facilitation of the PAR response was predominant, inhibition did take place at intervals of 80 ms and 160 ms. The situation was very different in subject P26 in whom the PAR was only facilitated from 0.2-10 ms and all other intervals caused inhibition. Facilitation was only seen in PAR if the TMS pulse was given at 10 ms, at all intervals later than this only inhibition of the PAR response was seen.

The compiled data in the scatter plot of figure 6.5 shows immediately that the y-values, the percentage change in PAR response is four-fold less in these subjects than in the non-SCI subjects (figure 6.5).

6.4 Discussion

TMS study

Conditioning a test evoked PAR response by TMS resulted in facilitation of the PAR response. Facilitation started when the TMS preceded DPN stimulation by 25-50 ms, reached a peak for near simultaneous stimuli and was absent when TMS occurred after DPN stimulation. The peak of facilitation was greater than 200% increase in the PAR for the non-SCI subjects. In comparison, the facilitation in the SCI subjects was only about 50% but the time course of facilitation was similar- perhaps reflecting damage to the descending corticospinal neurons mediating the response to TMS as well as cortical changes. These findings suggest that such condition-testing will be useful for assessing the efficacy of any technique aimed at restoring normal function of the bladder and sphincter function in spinal cord injury.

6.5 Conclusion

Although the use of TMS has to be further investigated but it may be speculated that this method has confirmed that descending pathways (corticospinal drive) are excitatory and that inhibition occurs at a segmental level involving sacral interneurones. Discrepancies (discomplete SCI subjects) between neuropathological and clinical findings in paralysis after spinal cord injury (SCI) suggest a niche for this type of improved functional assessment tool which may then add a much needed resolution to the clinical evaluation of residual supraspinal motor control in the absence of voluntary movement. Noninvasive treatment approaches may be indicated for these subjects such as training to augment volitional abilities. Persons with such an SCI, in addition to gaining some control over their movement, might require less medication with its inherent side effects.

Further experiments are now being conducted to identify the site(s) of interaction of these pathways and to determine whether the aberrant neural mechanisms in SCI might be responsive to repetitive TMS by tapping into neural plasticity for restoring normal facilitatory function.

Chapter 7

Relationship Between Neurophysiological Measures And Standard Neurological Assessment

7.0 Introduction

The previous experimental chapters have described research into standardizing a technique that combined routine neurophysiological tests with urodynamics. This involved the testing of the activity of the segmental sacral pudendo-anal reflex response (PAR) with bladder function as a measure of the guarding response (GR); and also explored was the volitional aspect of the GR by measuring the activity of the PAR response with voluntary squeeze of the pelvic floor and sphincters. The underlying aim of these experiments being to develop this somato-visceral neurophysiological tool to ascertain neurological pelvic dysfunctional deficits resulting from spinal cord injury (SCI), in order to address those deficits of the ASIA/IMSOP impairment scale. The ASIA is the standard most commonly used neurological assessment examination against which all other functional tests are measured in spinal injury. However it is not always consistently rated and neither does it assess autonomic function. In the development of this tool it is necessary to establish its sensitivity and correlation with the ASIA.

7.1 Aim

To establish the relationship between two spinal cord injury assessment techniques, one is the widely used neurological examination ASIA/IMSOP Impairment Scale and the second is the PAR somato-visceral assessment tool in order to evaluate the potential niche of this new modus operandi in the current milieu of assessment techniques.

7.2 Methods

Statistical analyses were performed to compare the different PAR response parameters with the ASIA grades and in some cases the motor and sensory components of the ASIA impairment scale (motor scores, light touch and pin prick scores). Significant correlation was shown by the Spearman correlation coefficient, rs with 95% confidence intervals and 2-tail p values. Parameters for comparison included, latency of the PAR responses, normalised PAR responses modulated by end fill volume (PARefv), voiding or NDO (PARvoid/ndo), bladder capacity (BC)and voluntary contraction of the pelvic floor/sphincters (PARvc).

7.3 Results

7.3.1 Latency Of The Pudendo -Anal Reflex Response

There was no significant correlation between the ASIA grades and the normalised latency of the PAR response tested at end fill volume (figure 7.0: rs=0.06, p=0.7) or during voiding or neurogenic detrusor overactivity (figure 7.1: rs=0.2, p=0.3). Although both parameters had positive relationships with the degree of neurological impairment such that the less the impairment, the longer the latency.

7.3.2 Compilation Of Pudendo -Anal Reflex Responses During Urodynamics

Data from chapters 3 and 4 were combined for the non-SCI subjects in figure 7.2 to show the change and polarity of the normalised PAR activity with the micturition cycle. Figures 7.3 and 7.4 show graphical representations of the normalised PAR responses for both filling cystometry and voiding for iSCI and cSCI subjects respectively. The normalised PAR responses elicited at end fill volume were statistically different ($p < 0.0001$) to the PAR responses tested during voiding cystometry in the non-SCI

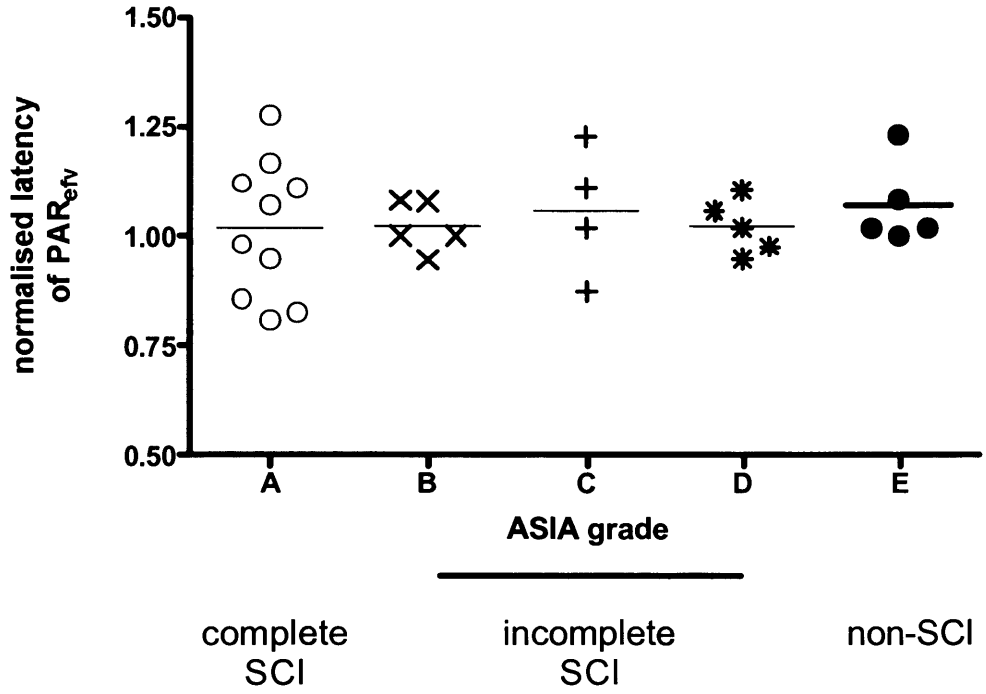


Figure 7.0 **Normalised Latency Of The Pudendo-Anal Reflex Response Tested With Bladder Filling Cystometry In Relation To ASIA Grade Classification.**

The graph shows the relationship between the normalised latency of the PAR responses tested with bladder filling (PARefv) and subjects as classified by their ASIA Impairment Scale grade. Spearman coefficient, rs= 0.06 (confidence intervals -0.3 to 0.4), indicating a positive relationsl between neurological status and the latency of PARefv response that is not significant p=0.73.

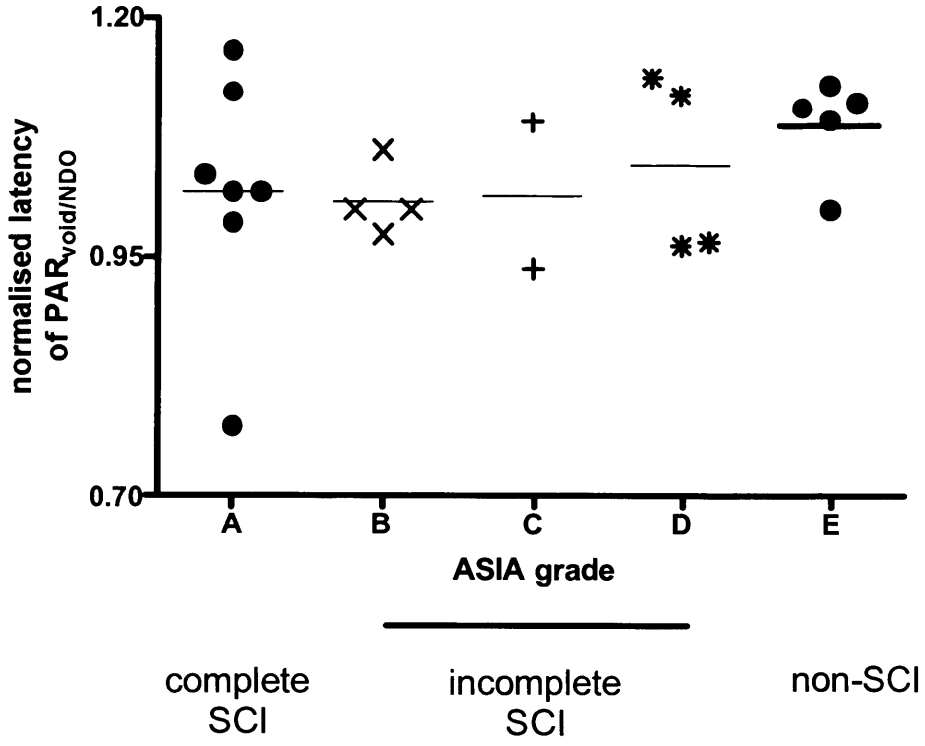


Figure 7.1 Normalised Latency Of The Pudendo-Anal Reflex Response Tested With Voiding Cystometry In Relation To ASIA Grade Classification.

The graph shows the relationship between the normalised latency of the PAR responses tested with voiding ($PAR_{void/NDO}$) and subjects as classified by their ASIA Impairment Scale grade. Spearman coefficient, rs= 0.2 (confidence intervals -0.2 to 0.5), indicating a positive relationship between neurological status and the latency of $PAR_{void/NDO}$ response that is not significant p=0. 35.

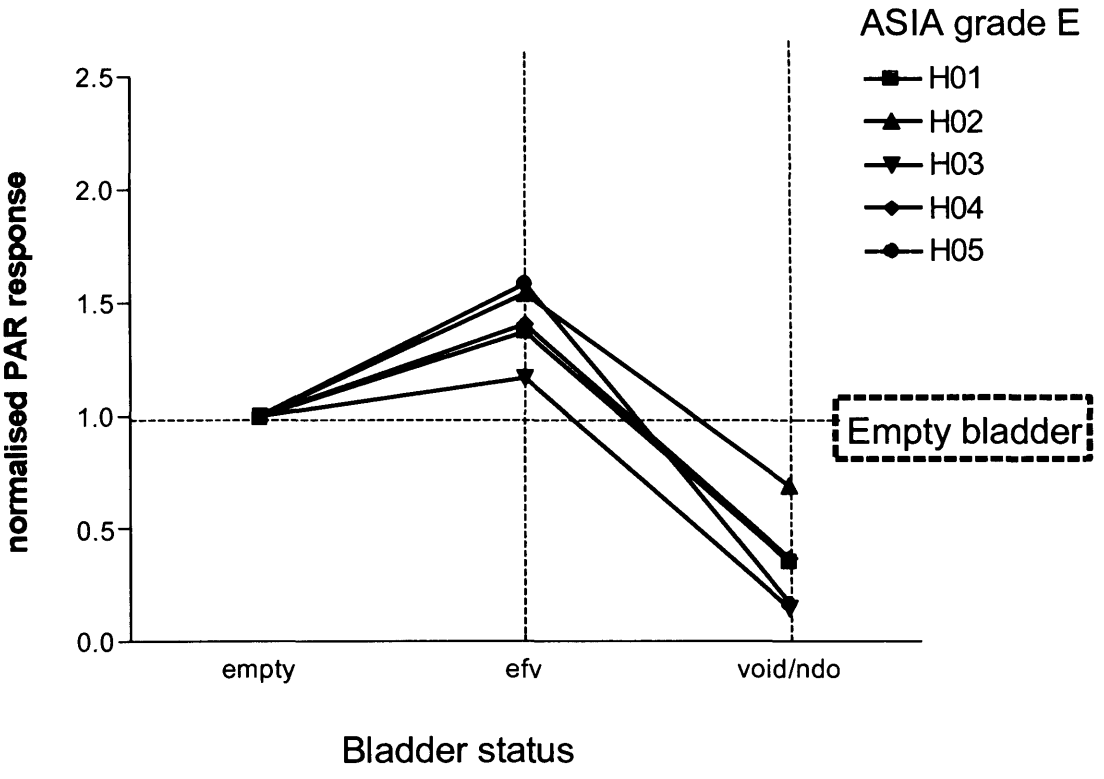


Figure 7.2 **Normalised Pudendo-Anal Reflex Responses Tested During The Micturition Cycle In Non-SCI Subjects**

The value y=1 corresponds to the PAR of an empty bladder to which each PAR response is standardised (normalisation). The x-axis represents the 3 phases of the bladder during one micturition cycle with an empty bladder followed by PARefv and PARvoid/ndo. The line connecting these points is not based on continuous data and is there simply to give a guide to the direction of amplitude and polarity of the change in GR as indicated by the PAR activity. In the legend H01 to H05 signifies anonymous identification tags for the 5 non-SCI subjects.

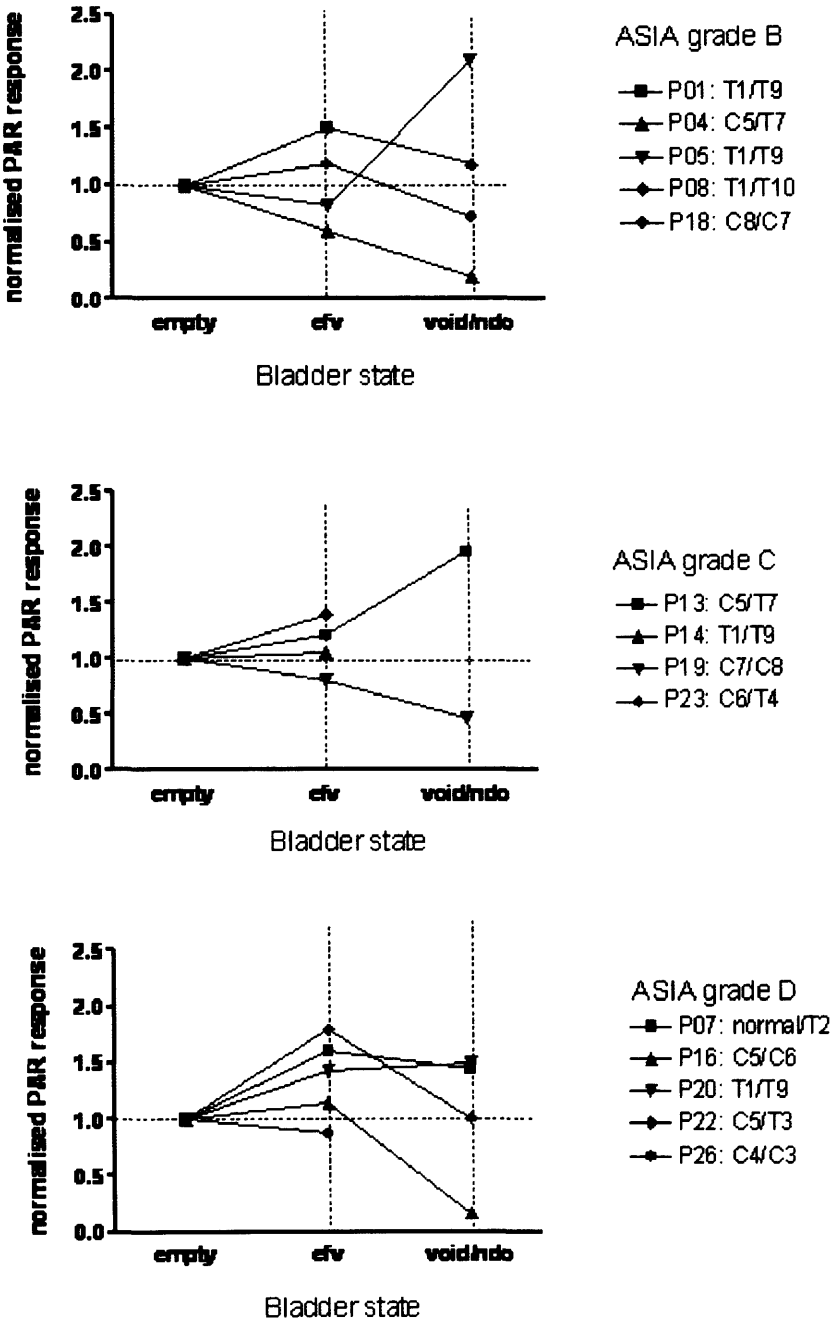


Figure 7.3 Modulation Of The Normalised Pudendo-Anal Reflex Responses With Bladder Function In Incomplete SCI Subjects

PAR responses representing the GR in iSCI subjects (coded with P followed by a numerical digit) graded ASIA B, C and D with their neurological level of injury (motor/sensory) in the legend taken at points during the micturition cycle: PARefv and PARvoid/ndo indicated with dashed lines. The line connecting these points is not based on continuous data and is simply to give a guide to the direction of amplitude and polarity of the change in GR. The value y=1 corresponds to the PAR of an empty bladder to which each PAR response is standardised (normalisation). If PARndo was taken several times, the maximum value was plotted.

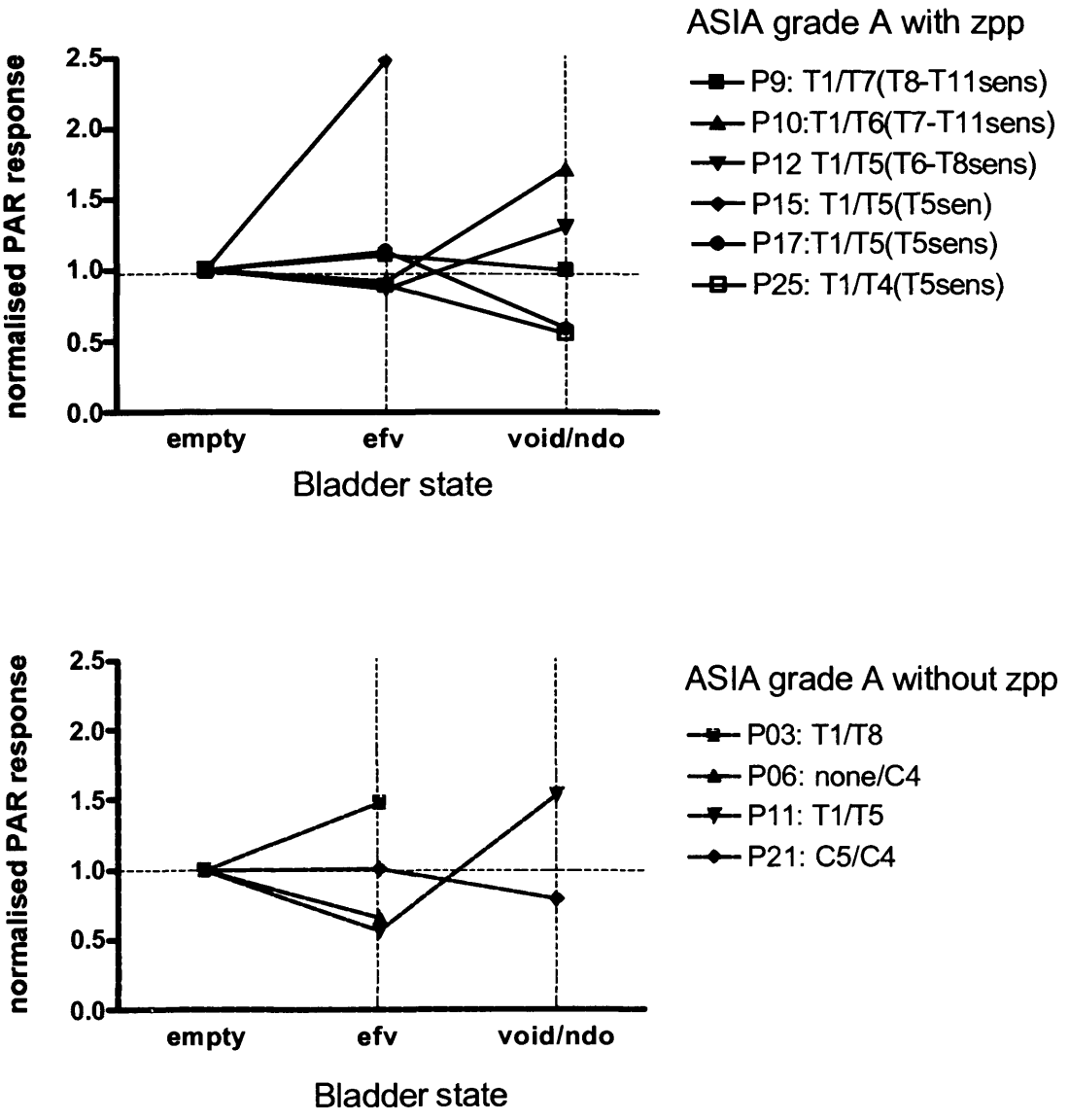


Figure 7.4 **Modulation Of The Normalised Pudendo-Anal Reflex Responses With Bladder Function In Complete SCI Subjects**

PAR responses representing the GR in cSCI subjects graded ASIA A and tagged with 'P' followed by a number (preserving patient anonymity) with their neurological level of injury (motor/sensory) in the legend with zone of partial preservation (zpp) in brackets in the right graph. The graph on the left has subjects with no zpp. PAR responses are taken at points during the micturition cycle: PARefv and PARvoid/ndo indicated with dashed lines. The line connecting these points is not based on continuous data and is simply to give a guide to the direction of amplitude and polarity of the change in GR. The value y=1 corresponds to the PAR of an empty bladder to which each PAR response is standardised (normalisation).

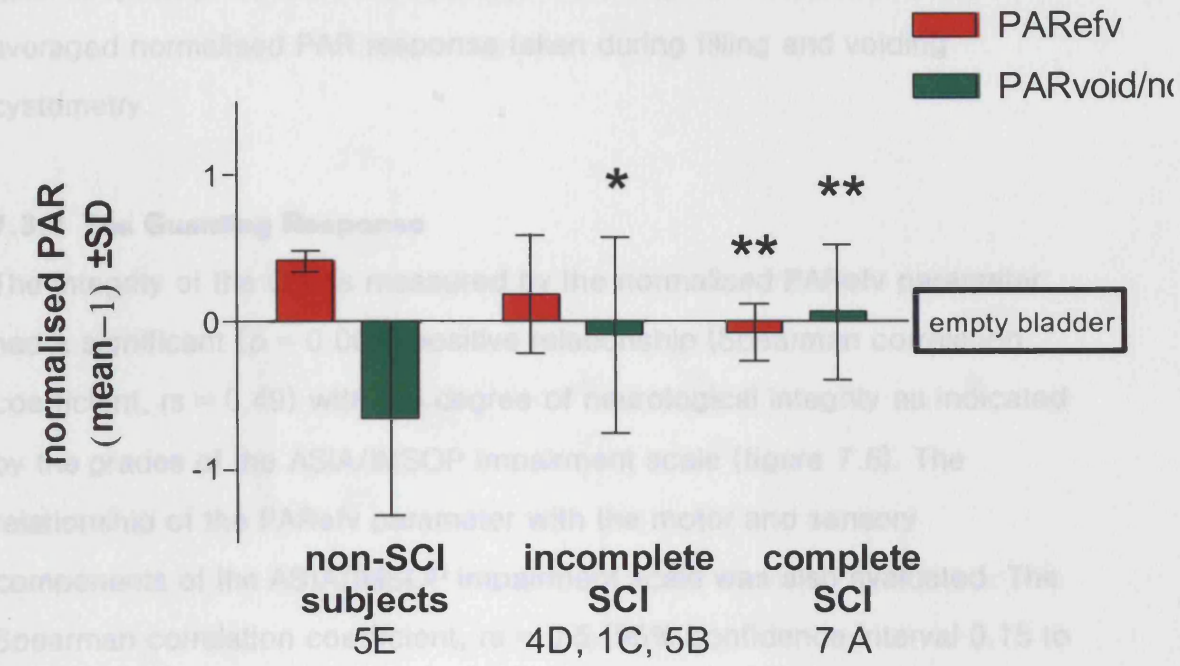


Figure 7.5 Averaged Normalised Pudendo-Anal Reflex Responses Modulated With Bladder Function In The 3 Cohorts

Shows the mean normalised changes in the peak to peak amplitude of the pudendo-anal reflex ([mean-1] ±SD) at end fill volume (EFV) and voiding (or neurogenic detrusor overactivity (NDO) in the case of the two spinal cord injury (SCI) groups). Subjects with a complete spinal lesion have little or no guarding reflex (red bars) compared to non-SCI subjects (denoted by **, p =0.002) whereas incomplete subjects have a very variable reflex. This variability probably reflects the wide range of neurological impairment in incomplete subjects. In subjects with a spinal injury the PAR change (green bars) reflects the presence of sphincter dyssynergia (denoted by * p=0.01 and ** p=0.005).

subjects, but were not significantly different for either of the SCI groups (iSCI subjects p=0.3; cSCI subjects p= 0.4). Figure 7.5 combines the averaged normalised PAR response taken during filling and voiding cystometry.

7.3.3 The Guarding Response

The integrity of the GR as measured by the normalised PARefv parameter had a significant (p = 0.007) positive relationship (Spearman correlation coefficient, rs = 0.49) with the degree of neurological integrity as indicated by the grades of the ASIA/IMSOP impairment scale (figure 7.6). The relationship of the PARefv parameter with the motor and sensory components of the ASIA/IMSOP impairment scale was also evaluated. The Spearman correlation coefficient, rs = 0.5 (95% confidence interval 0.15 to -0.7) indicated a positive significant (p = 0.0061) relationship between PARefv and motor score component (figure 7.7) showing that higher value motor scores are associated with higher values in PARefv, i.e. increased integrity of the GR). For the light touch scores (both spinothalamic and dorsal columns): the Spearman correlation coefficient, rs = 0.52 (95% confidence interval 0.18 to -0.75) indicated a significant (p = 0.0038) positive relationship between PARefv and the sensory light touch score component of the ASIA/IMSOP (figure 7.8) showing that higher value light touch scores are associated with higher values in PARefv, i.e. increased integrity of the GR. The Spearman correlation coefficient, rs = 0.53 (95% confidence interval 0.19 to -0.7) indicated a significant (p = 0.0032) positive relationship between PARefv and the pin prick score (spinothalamic pathways) (figure 7.9) component of the ASIA/IMSOP, showing that higher value pin prick scores are associated with higher values in PARefv, i.e. increased integrity of the GR.

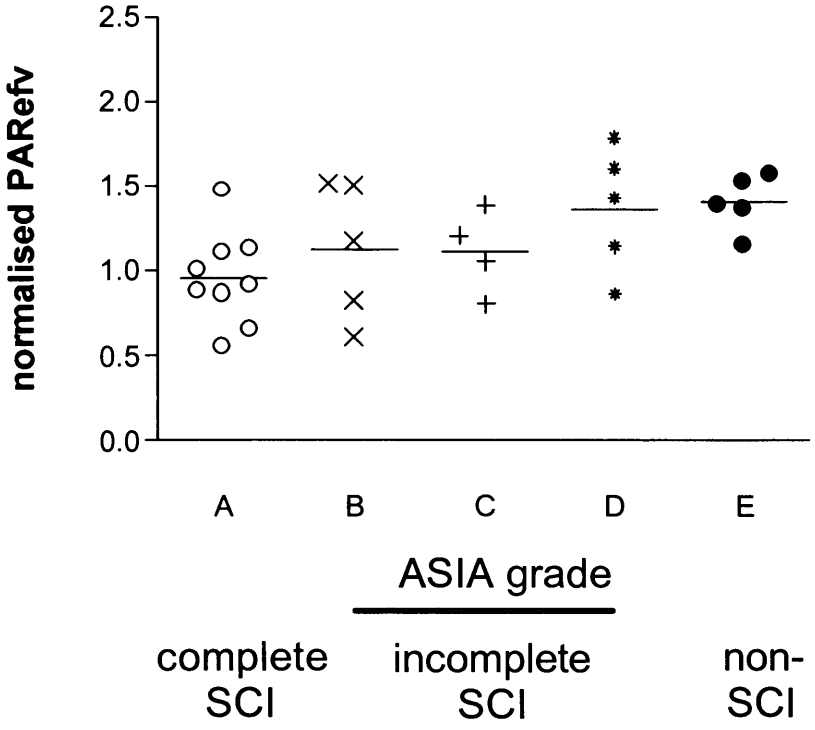


Figure 7.6 **Correlation Of The Normalised PARefv Parameter With The ASIA/IMSOP Impairment Scale**

The Spearman correlation coefficient, rs = 0.49 (95% confidence interval 0.13 to 0.73) indicates a highly significant (p = 0.007) positive relationship between PARefv and neurological status as classified by ASIA grades showing that the greater the neurological status (eg ASIA E) the better the GR, as measured by the PAR activity at end fill volume.

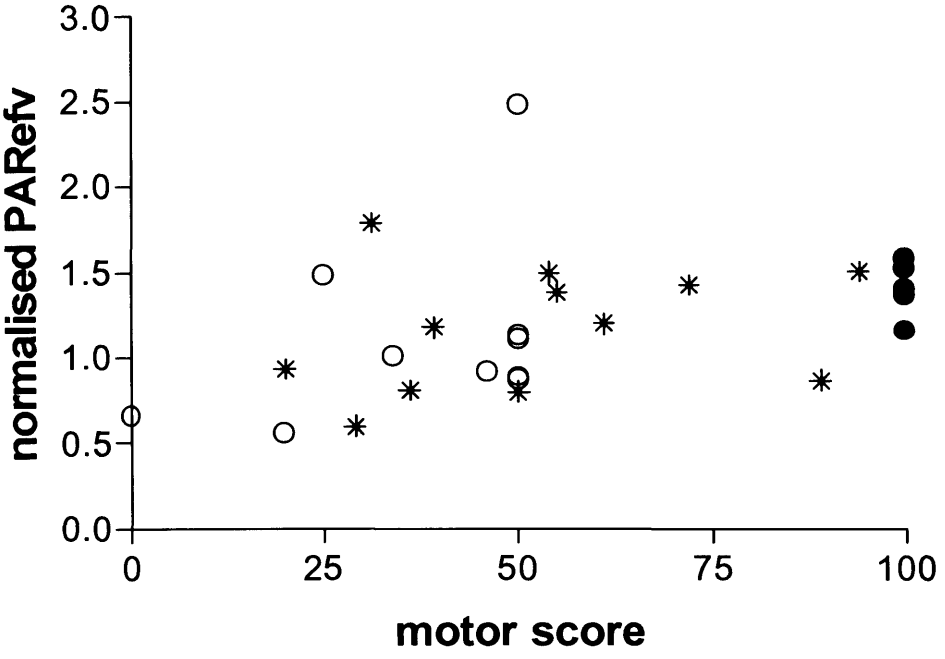


Figure 7.7 Correlation Of PARefv With The Motor Score Component Of The ASIA/IMSOP Impairment Scale Examination

Filled circles- non-SCI subjects
Stars- incomplete SCI subjects
Open circle- complete SCI subjects

Spearman correlation coefficient, rs = 0.5 (95% confidence interval 0.15 to -0.7), indicates a significant (p = 0.0061) positive relationship between PARefv and the motor score component of the ASIA/IMSOP impairment scale indicating that higher value motor scores are associated with higher values in PARefv, i.e. increased integrity of the GR

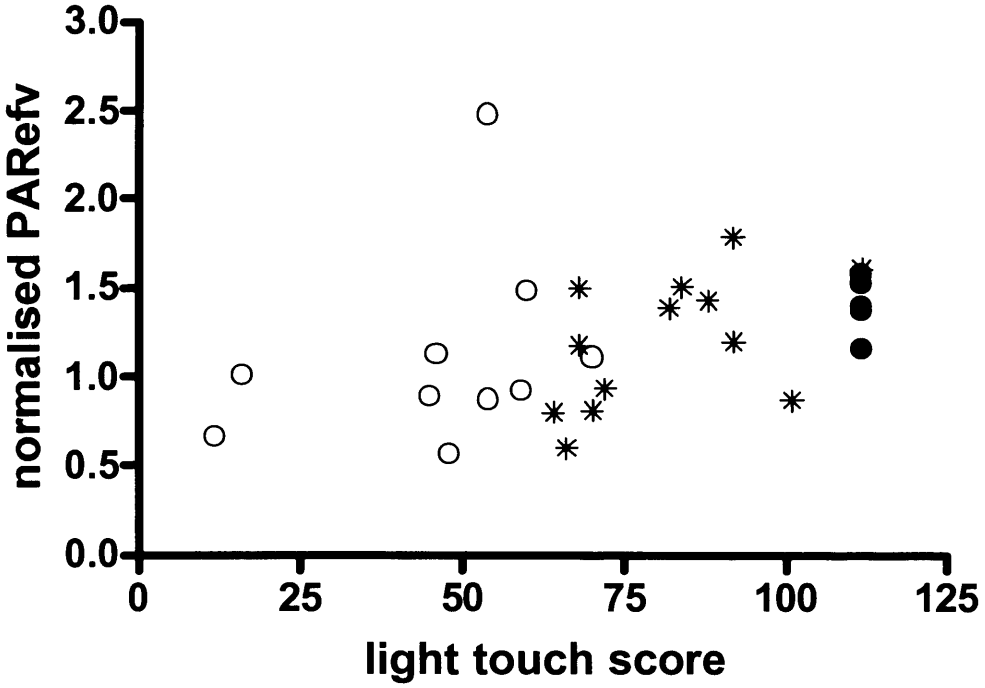


Figure 7.8 **Correlation Of PARefv With The Sensory Component Of The ASIA/IMSOP Examination Parameter, The Light Touch Score**
Filled circles- non-SCI subjects
Stars- incomplete SCI subjects
Open circle- complete SCI subjects
Spearman correlation coefficient, rs = 0.52 (95% confidence interval 0.18 to -0.75), indicates a significant (p = 0.0038) positive relationship between PARefv and the sensory light touch score component of the ASIA/IMSOP showing that higher value light touch scores are associated with higher values in PARefv, i.e. increased integrity of the GR

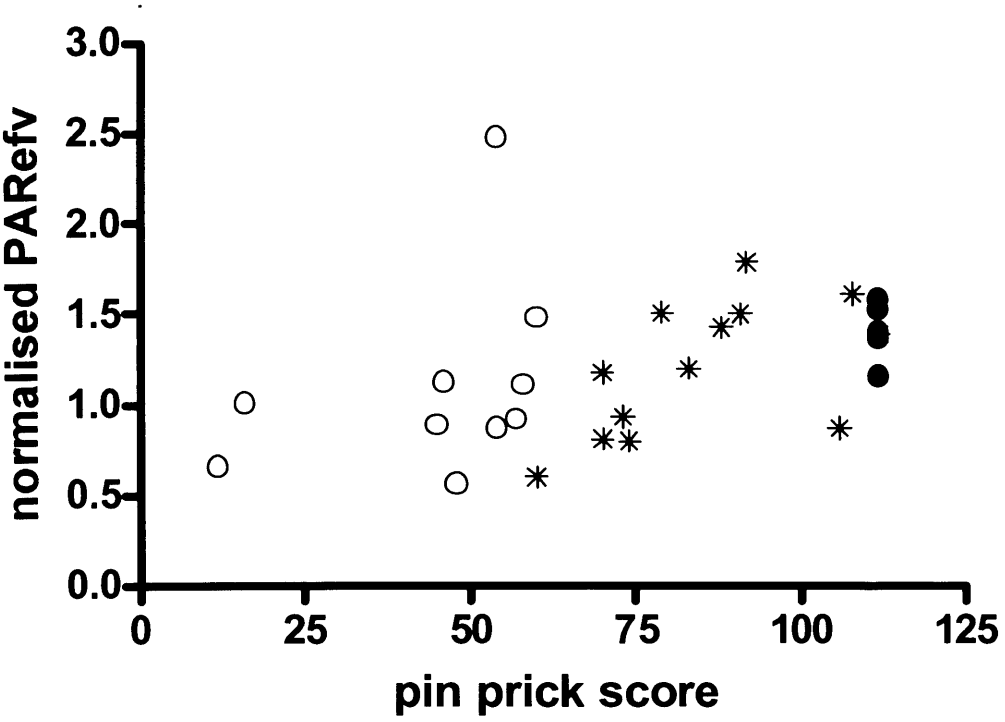


Figure 7.9 Correlation Of PARefv With The Sensory Component Of The ASIA/IMSOP Examination, The Pin Prick Score

Filled circles- non-SCI subjects
Stars- incomplete SCI subjects
Open circle- complete SCI subjects

Spearman correlation coefficient, rs = 0.53 `(95% confidence interval 0.19 to -0.7), indicates a significant (p = 0.0032) ,positive relationship between PARefv and the pin prick score component of the ASIA/IMSOP showing that higher value pin prick scores are associated with higher values in PARefv, i.e. increased integrity of the GR

7.3.4 Bladder Capacity

Bladder capacity showed a significant a (p = 0.0003) positive correlation (Spearman coefficient, rs = 0.6 (95% confidence interval 0.33 to 0.81) with the degree of neurological intactness as measured with the ASIA/IMSOP scale (figure 7.10), indicating that those with higher bladder capacity had better neurological integrity.

7.3.5 Suppression Of The Guarding Response

The degree of suppression of the GR during periods of NDO or voiding, as measured by the PARvoid/ndo parameter had a significant (p = 0.02) negative relationship (Spearman correlation coefficient, rs = −0.48) with the grades of the ASIA/IMSOP scale (figure 7.11), indicating those classified ASIA E have very low PAR activity during voiding, showing good suppression of the EAS muscle activity which allowed unobstructed voiding.

The relationship of the PARvoid/ndo with the motor and sensory components of the ASIA/IMSOP scale was also evaluated. The parameter PARndo had a significant (p = 0.02) negative relationship (Spearman correlation coefficient, rs = −0.49, 95% confidence interval −0.76 to −0.07), with the motor score component of the ASIA/IMSOP (figure 7.12), indicating that higher value motor scores are associated with lower values in PARndo, i.e. greater suppression of EAS activity during voiding. PARndo also had negative correlation (light touch: Spearman correlation, rs = −0.32, (95% confidence interval −0.66 to 0.14); pin prick: Spearman correlation, rs = −0.3, (95% confidence interval −0.66 to 0.15) with the sensory components of the ASIA/IMSOP, but these were not significant correlations (figure 7.13 and 7.14).

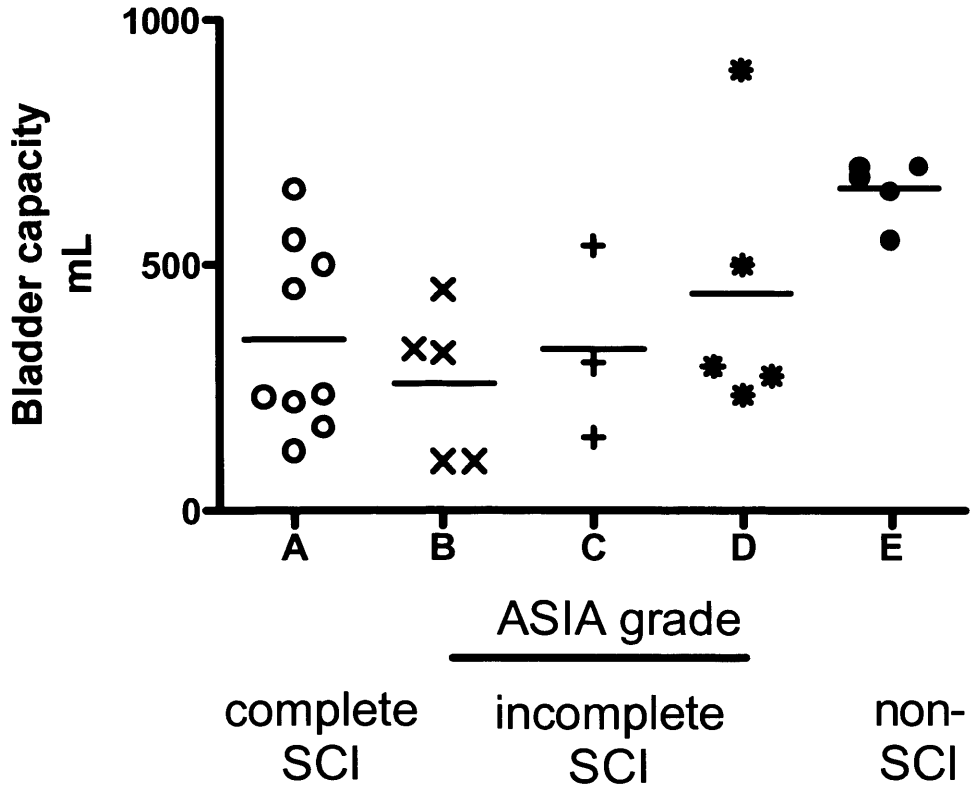


Figure 7.10 Correlation Between Bladder Capacities With ASIA/IMSOP Impairment Scale Grades

Spearman correlation coefficient, rs = 0.6 (95% confidence interval 0.3223 to 0.8149) indicates a positive relationship between bladder capacity and the ASIA grades of subject groups as assessed using the American Spinal Injuries Association (ASIA) impairment score of neurological dysfunction in spinal cord injury (AIS A-E), with a p = 0.0003 indicating the relationship to be highly significant, such that those classified as ASIA E have high bladder capacity.

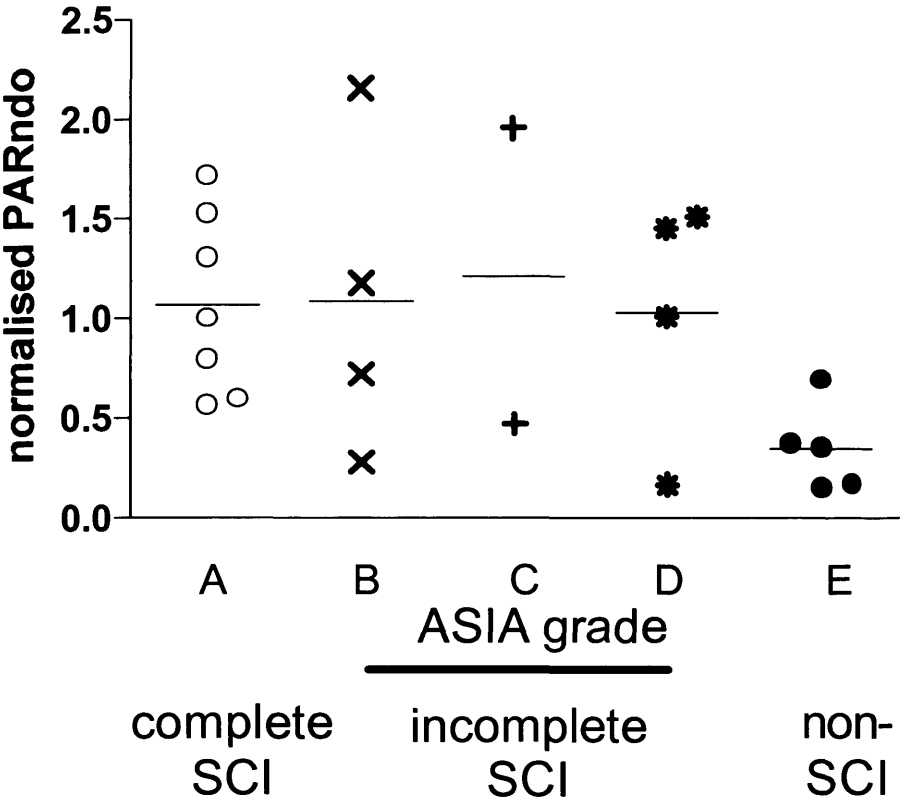


Figure 7.11 Correlation Of PARndo With The ASIA Grades Of The ASIA/IMSOP Impairment Scale

The Spearman correlation coefficient, rs = -0.48 (95% confidence interval -0.76 to -0.70), indicates a significant (p = 0.02) negative relationship between PARndo and the ASIA grades which was the result of ASIA E subjects having very low PAR activity during voiding, showing good suppression of the EAS muscle activity which allowed unobstructed voiding, with this PAR activity increasing with increasing neurological impairment.

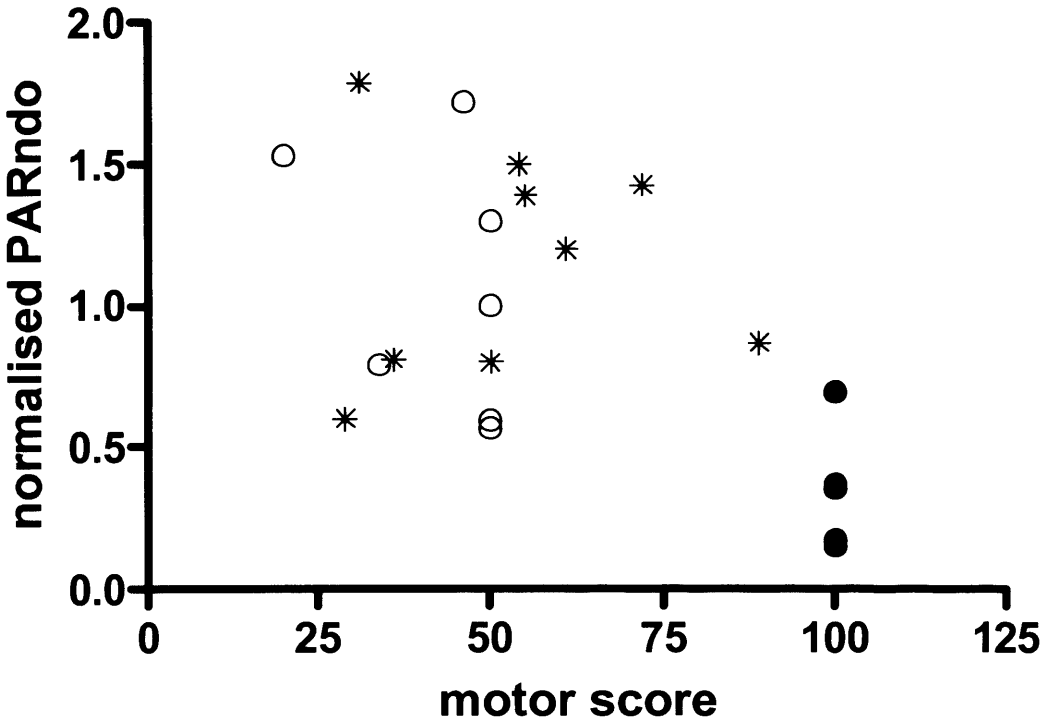


Figure 7.12 Correlation Of PARndo With The Motor Component Of The ASIA/IMSOP Examination, The Motor Score
Filled circles- non-SCI subjects
Stars- incomplete SCI subjects
Open circle- complete SCI subjects

Spearman correlation coefficient, rs = -0.49 (95% confidence interval -0.76 to -0.07), indicates a significant (p = 0.02) negative relationship between PARndo and the motor score component of the ASIA/IMSOP indicating that higher value motor scores are associated with lower values in PARndo, i.e. and therefore better suppression/inhibition of EAS activity during voiding.

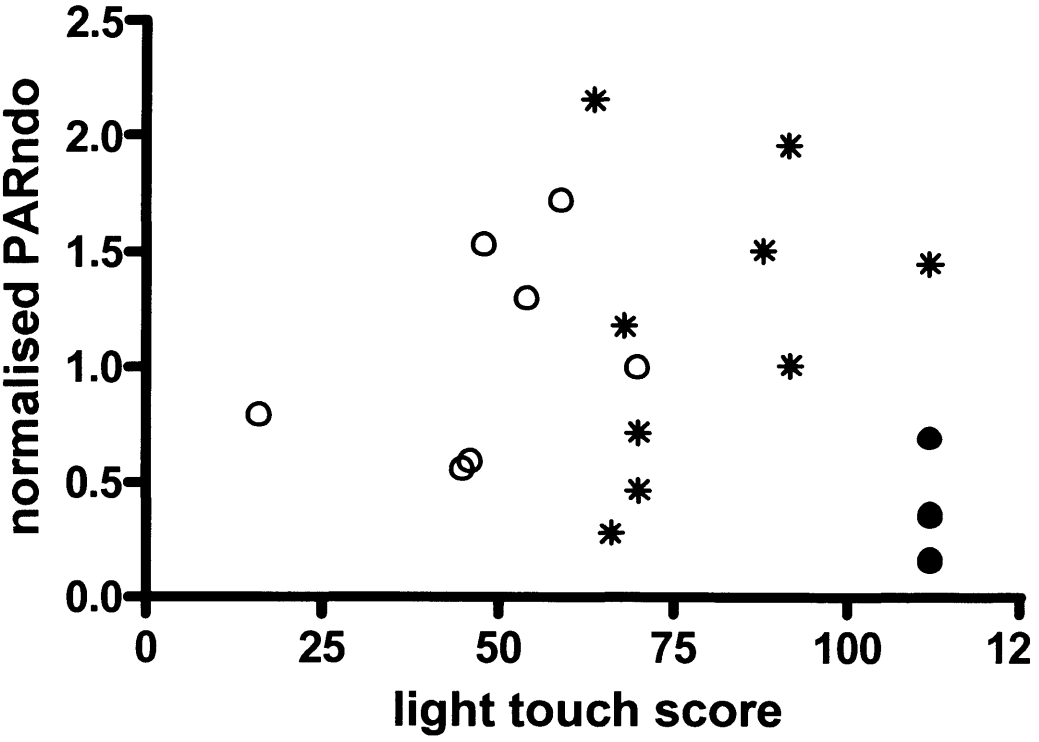


Figure 7.13 Correlation Of PARndo With The Sensory Component Of The ASIA/IMSOP Examination Parameter, The Light Touch Score
Filled circles- non-SCI subjects
Stars- incomplete SCI subjects
Open circle- complete SCI subjects

The Spearman correlation coefficient, rs = -0.32 (95% confidence interval -0.66 to 0.14) indicates a negative relationship between PARndo and the sensory light touch score component of the ASIA/IMSOP which is not significant $p = 0.15$

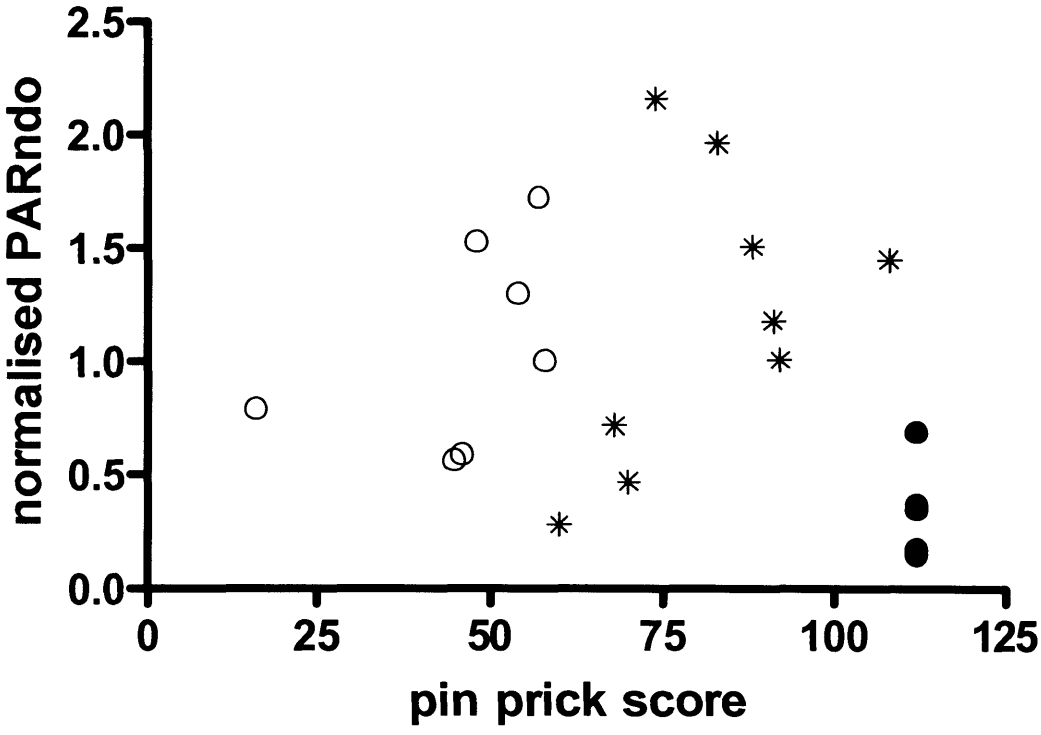


Figure 7.14 Correlation Of PARndo With The Sensory Component Of The ASIA/IMSOP Examination, The Pin Prick Score

Filled circles- non-SCI subjects
Stars- incomplete SCI subjects
Open circle- complete SCI subjects

The Spearman correlation coefficient, rs = -0.3 (95% confidence interval -0.66 to 0.15) indicates a negative relationship between PARndo and the pin prick score component of the ASIA/IMSOP which is not significant p =

Figure 7.15 shows the somato-vesical neurophysiological measure in a scatter plot with all participants in this study graded with their ASIA classification grade. This graph shows instantly the decreasing GR with the increasing impairment of the subject during filling cystometry, and the increased variability in iSCI subjects and prevalence of the detrusor sphincter dyssynergia in cSCI subjects during voiding cystometry.

7.3.6 Pudendo-Anal Reflex Response And Neurological Level Of Injury

Data from the iSCI subjects was pooled to investigate whether the level of injury (thoracic or cervical) influenced the two outcome measures: PARefv and PARndo (figure 7.16). This analysis could not be performed with the data from the cSCI group because all had thoracic injuries bar one. Cervical and thoracic breaks result in subjects with similar PARefv values. In this group of subjects PARndo was found to be significantly influenced by the level of injury, in that thoracic lesions appeared to elicit increased PARndo values. This analysis could not be performed with the data from the cSCI group because all had thoracic injuries bar one. Only half of the cSCI in our cohort with recordable PARndo values experienced DSD.

7.3.7 Modulation Of The Pudendo-Anal Reflex Response With Pelvic Floor And Sphincter Contraction

The modulation of evoked PAR response by voluntary contractions of the pelvic floor, termed PARvc was shown to have a highly significant (p = 0.0006) and positive relationship with the ASIA grades of the ASIA/IMSOP impairment scale (figure 7.17) as shown by the Spearman correlation coefficient, rs 0.6; and also with the motor component (figure 7.18, rs 0.4, p = 0.03) of the ASIA/IMSOP scale.

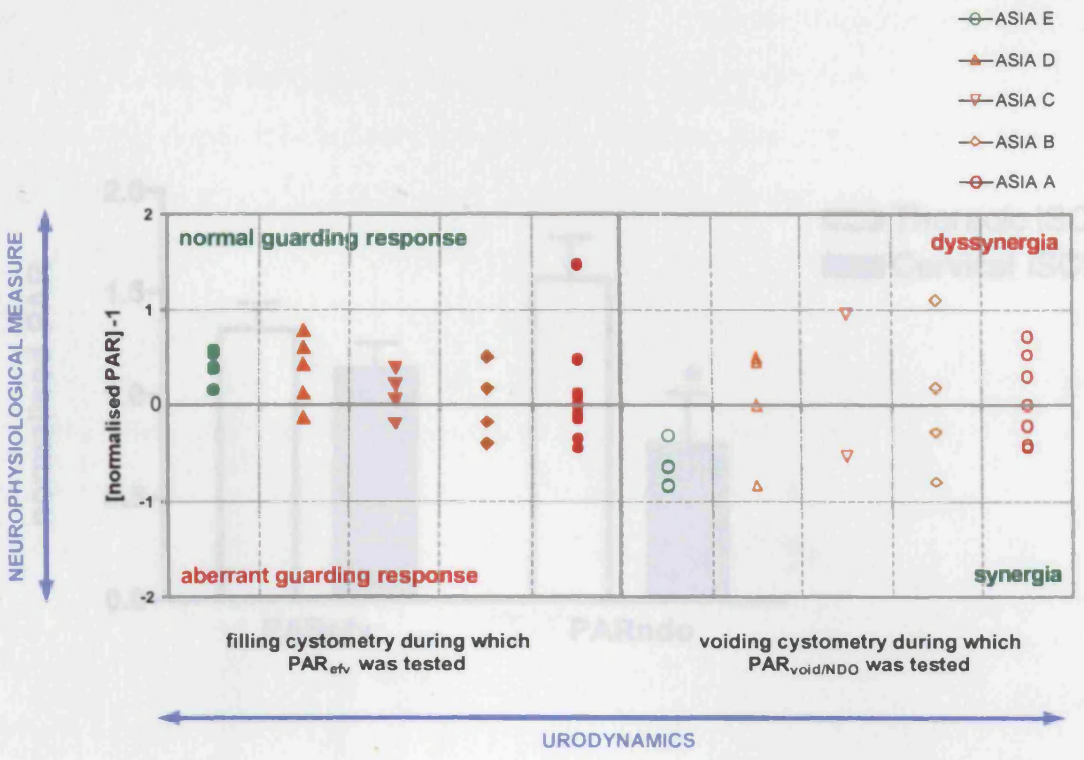


Figure 7.15 Somato-Vesical Neurophysiological Measure

Along the y-axis is the somatic measurement of the PAR. Along the x-axis is the urodynamic variable. In the 4 quadrants of the graph fall the subjects classified by their ASIA grades. In green letters are the normal manifestations of continence and competent bladder sphincter coordination. In the red letters are those expressions of pelvic dysfunction resulting from bladder disinhibition during filling cystometry and poor bladder sphincter coordination during voiding cystometry.

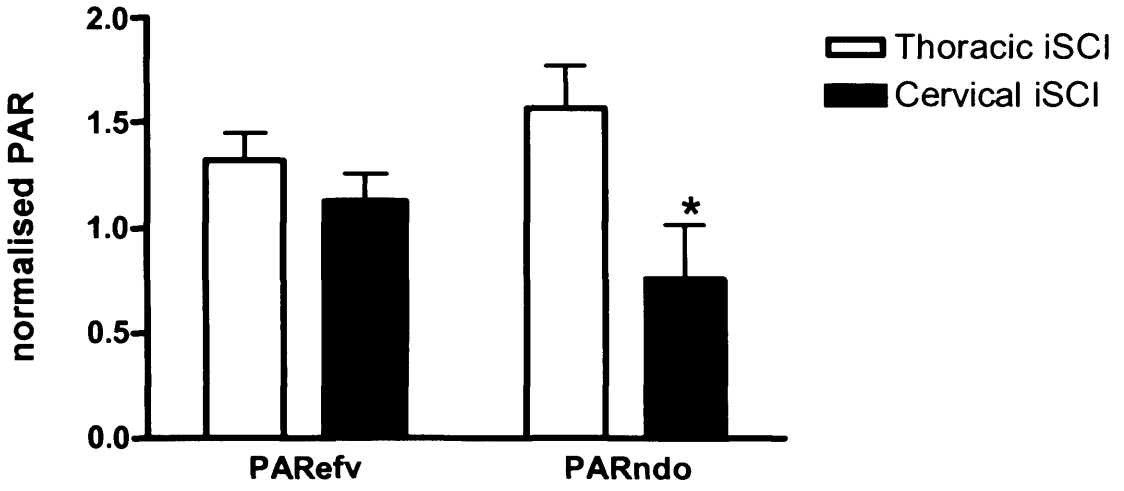


Figure 7.16 Effect of level of injury and the normalised PAR response for filling and voiding cystometry in iSCI subjects

Graphical data of PAR evoked at end fill volume, PARefv, and during neurogenic detrusor overactivity, PARndo, expressed as mean±sem for incomplete spinal cord injury subjects. The symbol denotes a statistical significance of, which indicates A significant difference between the mean PARndo for those subjects with thoracic injuries and those with cervical lesions and is shown by the symbol *, which denotes a significance of $p = 0.04$.

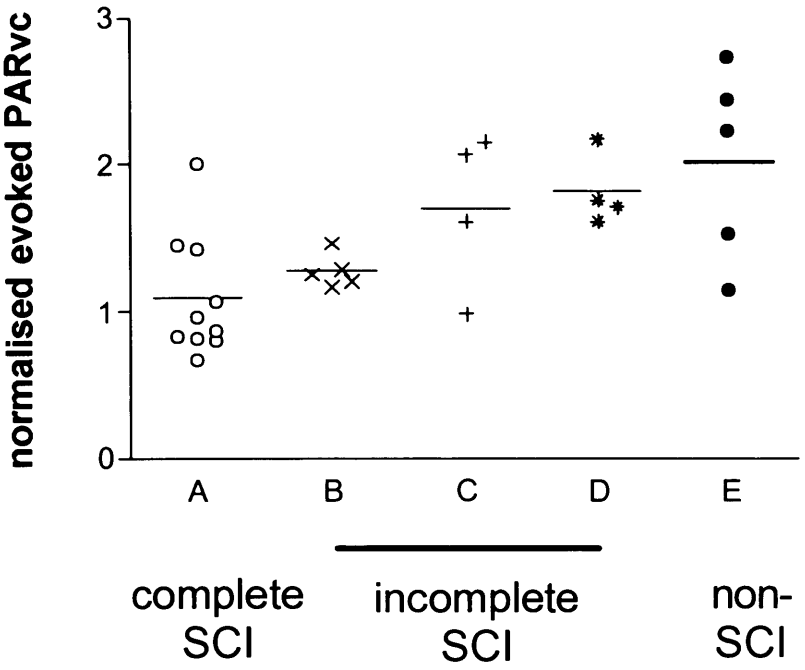


Figure 7.17 **Correlation Of The Normalised Pudendo-Anal Reflex Response Modulated With Voluntary Contraction Of The Pelvic Floor With ASIA/IMSOP Impairment Scale**

Peak to peak measure of pudendal-anal reflex response modulated with volitional effort at the y-axis (PARvc) against the ASIA grades of the ASIA/IMSOP Impairment scale at the x-axis.

The Spearman correlation coefficient rs = 0.6 (95% confidence internal 0.2 to 0.8) showed there to be a significant (p = 0.0006) positive relationship between PARvc and traditional ASIA grades

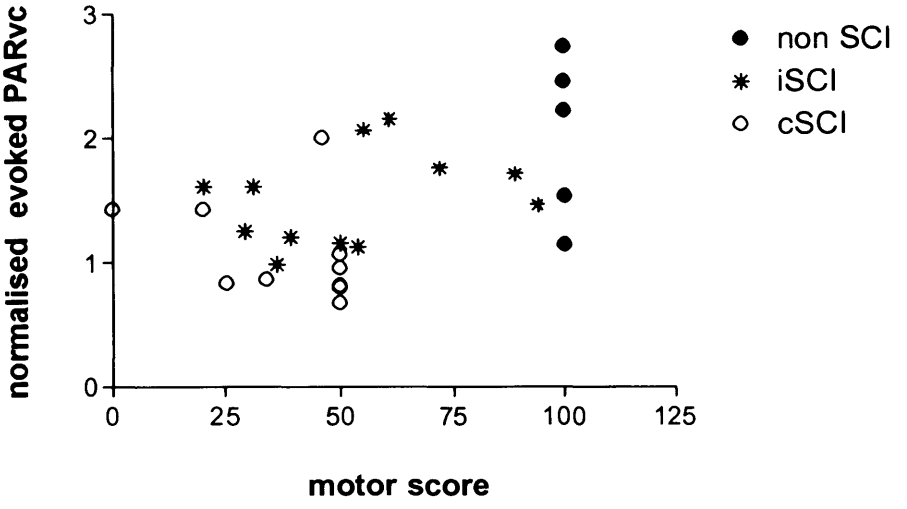


Figure 7.18 Correlation Between The Ability Of A Subject To Modulate Their Pudendo-Anal Reflex Response With Pelvic Voluntary Contraction And The Motor Score Element Of The ASIA/IMSOP Impairment Scale

Spearman correlation coefficient, rs = 0.4 (95% confidence intervals 0.08 to 0.71) indicates that a positive significant (p= 0.01) relationship exists between the PARvc (y-axis) and the motor score element of the ASIA/IMSOP Impairment scale.

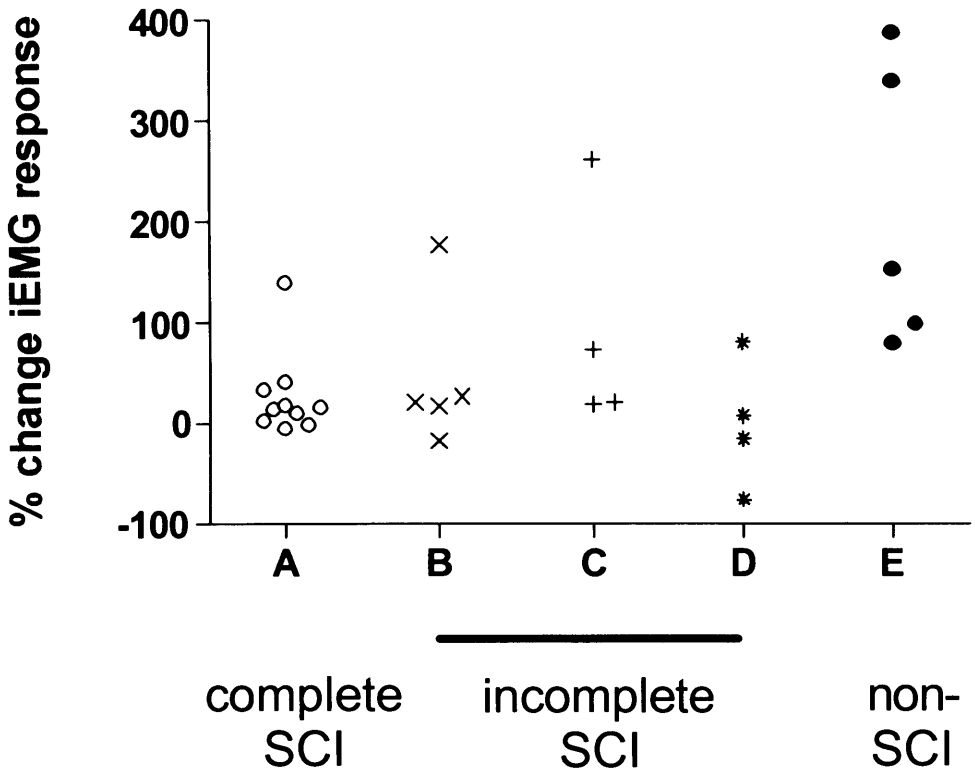


Figure 7.19 Relationship Between The Percentage Change In Integrated EMG Response Due To Volitional Effort And The Neurological Status Of A Subject As Assessed Using The ASIA/IMSOP Impairment Scale.

The Spearman correlation coefficient, rs=0.4 (95% confidence intervals 0.05 to 0.69) indicates that a positive significant (p = 0.02) relationship exists between the ability to contract the pelvic floor and the degree of neurological capacity of an individual.

Statistical analysis showed that although the more traditional technique of analyzing the percentage change in iEMG (figure 7.19) appeared to have a linear relationship with the ASIA/IMSOP Impairment Scale, it was not as highly significant a correlation (as shown by the Spearman correlation coefficient, rs 0.4, p=0.054).

7.4 Discussion

The PAR response appeared to reflect exactly the pelvic dysfunction of the subject. For example the maintenance of continence was accompanied by a PARefv>1 during filling cystometry indicating a sound guarding response, as did a PARefv<1 during filling cystometry was associated with low bladder capacities. The GR as measured by the PARefv parameter was found to be independant of the level of lesion in the iSCI subjects. A relationship between this parameter and the level of lesion in the cSCI subjects was not possible in this study, but would be interesting for a future study. As for voiding, low PARvoid/NDO values were associated with unobstructed voiding during and synergic bladder sphincter coordination, as were high PARvoid/NDO associated with obstructed voiding. Analysis illustrated that the PAR responses during filling cystometry and voiding cystometry were greatly different in non-SCI subjects, but very similar in SCI subjects.

The comparison between the ASIA/IMSOP impairment scale and the evoked PAR response compared sensory and motor assessments with somatovisceral assessment respectively, thus incorporating autonomic function. Both the PAR responses tested in bladder function showed good correlation with the ASIA grades. The PARefv parameter related well to all ASIA components inidcating it to be a good measure of the GR in both its afferent, in the sensory component, and its efferent limb, in the motor component. Whereas PARvoid/ndo only related well to the motor

component of the ASIA indicating the requirment of perhaps a more predominant motor component in the mechanism of suppressing or inhibiting the GR, to allow unobstructed voiding. Also increased

PARvoid/NDO vlaues were associated more closey with thoracic iSCI subjects rather than with cervical. The reason for this is not readily discernable. Resulting bladder capacities, a commonly used parameter in urodynamics showed good correlation with the ASIA/IMSOP impairment scale and the PARefv parameter.

The latency of the PAR response showed no relation to bladder function or the ASIA impairment scale. It could be that the sample size of this study was too small to discern any real trends.

7.4.1 Volitional Aspect Of The Guarding Response

The modulation of evoked PAR response by voluntary contractions of the pelvic floor, correlated more highly with the grades and the motor component of the ASIA than did the more traditional electromyographical method of assessment.

The level of injury appeared to significantly influence PAR activity during NDO, with those with thoracic lesions experiencing significantly greater DSD i.e. an inability to suppress the GR during periods of NDO than those subjects with cervical breaks. Our data in part supports that of Kyle and Dmochowski (2000) who showed that those with single level SCI had significant association between level of injury and type of voiding dysfunction.

7.5 Conclusion

Although neurophysiological somatovesical measures cannot replace neurological assessments they do highlight variability across the subjects. They can enhance the information amassed in several ways: neurophysiological testing of the evoked PAR response is able to demonstrate the presence of conduction in patients with no apparent function; it can be carried out frequently in situations of rapid change; it could prove to be useful in uncooperative or unconsious patients; and with further studies and more data it may be that this kinesiological somatovesical response may be able to give insights into causes of dysfunction or be able to predict the types of pelvic dysfunction associated with different types or degrees of SCI.

Chapter 8

General Discussion

8.0 Overview

A recent survey highlighted that the need for neural repair of pelvic function was of primary importance in the spinal cord injured (SCI) population (Anderson, 2004). A great deal of research is being done to develop a tool that could repair pelvic function. However there are no sufficiently sensitive detection techniques which might pick up regenerative or restorative effects elicited by such a tool.

Currently pelvic function assessment focuses on procedures such as urodynamics/ cystometry and anorectal monitoring. These are important in that they allow the identification of dangerously high bladder pressure conditions such as detrusor sphincter dyssynergia (DSD) and neurogenic detrusor overactivity (NDO) which can then be treated. However, in terms of potential to pick up neural repair, these procedures have a relatively low sensitivity and relevance to the current standards of neurological impairment testing. ASIA is the most commonly used neurological impairment test, but only provides verification of the neurological level of injury (NLI) in terms of motor and sensory deficits. This leaves the status of pelvic function wholly undetermined.

Thus there is a real need for a robust impairment grading and scoring system for pelvic dysfunction which can then be implemented prior to, and post, neural interventions, to assess their success.

Park *et al.* (1997) suggested that the key to bladder control may lie in the assessment of the external urethral sphincter (EUS) which is the result of voluntary somatic neuromuscular control and involuntary autonomic

regulation. And it's known that routine clinical neurophysiological examination of the segmental sacral reflexes would lead to information about the innervation of bladder and EUS (Wyndaele, 1997). As such these reflexes may provide a measure of the integrity of the guarding response (GR). Based on this, this thesis has aimed to combine the techniques of basic cystometry with that of evoked sacral reflex potential, to develop a standardised somatovisceral neurophysiological measure which may have advantages over the current procedures of assessment in SCI and which may also fill a role in the assessment of neural pelvic repair techniques.

8.1 Thesis Overview

Chapters 1 and 2 stated the clinical problem and presented a study design to address it. In chapters 3 and 4 the PAR response was tested kinesiologically with bladder function, to assess it as a measure of the guarding response, GR and tests its repeatability. Chapters 5 and 6 investigated the volitional aspect of continence by relating the modulatory capacity of descending pathways and also transcranial magnetic stimulation to the PAR response. The data from the preceding experimental chapters was collated and correlated with the currently most widely used neurological impairment scoring system of SCI to assess whether the presented somatovisceral neurological measure was as good a measure of SCI as the ASIA impairment scale. This general discussion aims to give a preliminary evaluation of this somatovesical neurophysiological assessment tool of SCI recommending future work to ascertain further insight into its potential role in neural functional repair studies.

8.2 Summary Of Findings

By standardisation of the sacral somatic reflex elicitation this work has confirmed the modulation of the pudendo-anal reflex (PAR), by bladder function. And for the first time both the integrated EMG and PAR response

has been shown to be modulated by voluntary effort in SCI. Of these two assessments techniques of voluntary effort, the PAR response has greater sensitivity for the completeness of lesion. Detecting such partial preservation of cortical motor influences was possible even in some patients classified neurologically as ASIA A- a finding that opens up rehabilitative opportunity for this group of subjects. And finally it has been shown that using TMS in the context of condition-testing will be useful for assessing the efficacy of any technique aimed at restoring normal function of the bladder and sphincter function in spinal cord injury.

Thus this study has shown that the aberrant sacral reflexes controlling lower urinary tract function in spinal cord injury can be modulated by residual involuntary (guarding reflex) actions as well as voluntary descending supra-spinal motor effects by interacting with segmental autonomic and somatic influences. For convenience, the pudendo-anal reflex (PAR) has proven to be one of the easiest and most useful sacral somatic reflexes to test.

8.3 The Reliability And Relevance Of The Pudendo-Anal Reflex Response

8.3.1 *Surrogacy*

The pudendo-anal reflex response (PAR) was used as a surrogate marker for the pudendo-urethral reflex response (PUR), a choice that is substantiated by extensive anatomical and neurophysiological evidence (Vereecken and Verduyn, 1970, Bradley and Teague, 1972 (cats); Tomohiko et al, 1982 Barrett, 1980; Perkash, 1980; Podnar and Vodusek, 2001, Wenzel et al. 2006 (cats and humans)).

8.3.2 *Optimisation Of Pudendo-Anal Reflex Response*

Optimal recruitment of the pudendo-anal reflex was achieved using a condition-test paradigm to stimulate the dorsal penile (exclusively pudendal sensory nerves) with pairs of electrical pulses through skin electrodes. We have confirmed the results of Rodi and Vodusek (1995) while they found that the best recruitment of Onuf's motoneurones in subjects with varying degrees of spinal completeness was achieved when the double-pulse interval was 3 ms, we found it to have a lower range between 1-2 ms. Although an isolated constant current stimulator was used for the DPN stimulation there was a great deal of variability between subjects in the PAR traces. This was attributed to normal anatomical and physiological variability and was corrected with the normalisation procedure which allowed the comparative analysis of the responses.

8.3.3 *Monitoring*

The choice of using an anal plug electrode was to mainly avoid discomfort in the non-SCI subjects (and the iSCI subjects) that had sensation and would find needle EMG unpleasant. Needle EMG is known to be useful in diagnosis (Kiff and Swash, 1984), to analyse muscle potentials, which is necessary for distinguishing between neurogenic and myogenic lesions - all of which was unnecessary for the aim of this study. Also our choice of plug electrode over needle to monitor the PAR was further supported (Wiesner and Jost 2000) because more motor units are registered, and thus responses with the shortest latency are gauged such that a composite picture of muscle activity was provided (Gee *et al.*, 2000).

8.3.4 *Latency Of The Pudendo-Anal Reflex Response*

The bulk of studies performed look at the latency of the sacral reflex response using needle/surface EMG (Garry et al 1959, Nordling and Meyhoff 1979, Krane and Siroky 1980, Siroky and Krane 1982, Rodi and

Vodusek 1995, Jost and Schimrigk 1994). The latency of the PAR response showed no correlation with either bladder function or degree of neurological deficit as classified using ASIA grades. This finding supports those of Rodi and Vodusek (1995). As mentioned previously one of the sacral reflexes, the bulbocavernosus reflex, BCR is used as the clinicians tool to assess integrity of S2–S4 reflex arc. Rodi and Vodusek (1995) demonstrated in patients with neuropathy known to abnormally lengthen BCR latencies, the specificity and sensitivity of the latency test was not proven satisfactory enough for clinical relevance.

Latency of the PAR response was however found to be consistently modulated by voluntary contraction of the pelvic floor across the subjects. This was not so surprising given that it is known that when an increasing stimulus is given, as the amplitude of the response increases so will its latency decrease.

8.4 Reliability Of The Pudendo-Anal Reflex Response

The significant reproducibility of the data (both PARefv and PARndo) presented here is supported by Rodi and Vodusek (1995) who found double pulse stimulation to be a reliable predictor of complete sacral reflex arc lesions, giving reproducible sacral reflex responses. This standardisation method of optimal recruitment and normalisation of the evoked PAR response with bladder function has proven this somatovisceral measure a robust parameter in repeatability studies – which is of high priority in the criteria of a potential assessment technique of SCI.

8.5 Sensitivity And Relevance Of The Pudendo-Anal Reflex Response

Sensitivity of the PAR response was demonstrated when the supra-spinal modulation of the guarding response during voluntary effort was

investigated; and also by the correlation of the somatovisceral measure with the AISA/IMSOP Impairment scale.

8.5.1 *Volitional Aspect Of The Guarding Response*

Although most of the neural circuits involved in the normal control of the bladder are autonomic, continence is very much a function of volitional control. To re-cap, the guarding response is the progressive involuntary increase in sphincter activity that ensures continence as the bladder fills. When the sensory threshold of bladder fullness is reached this sphincter activity increases even further becoming a conscious and voluntary phenomenon as the person actively tries to remain dry in juxtaposition to a bladder wanting to empty (Park et al. 1997). Thus voluntary contraction of the pelvic floor muscles/EUS/EAS plays an important role in normal continence mechanisms particularly during postponement of voiding and that such contractions probably inhibit the parasympathetic reflex pathways within the spinal cord to suppress premature voiding contractions, makes the qualitative assessment of this volitional control of interest.

The normal evoked PAR response was clearly facilitated by voluntary contractions of the pelvic floor. High correlation between the bladder capacities with the percentage change in PAR response modulated by pelvic floor contraction demonstrated the role played by volition in the GR and in maintaining healthy bladder volumes. This technique had a higher correlation with ASIA grades than did the more traditional method of assessing changes to EMG activity by analyzing integrated EMG (iEMG). The change in evoked PAR also showed greater sensitivity for the completeness of lesion, being able to discern differences between all three subject groups. Whereas the method of iEMG was able to discern only the cSCI subjects from the other subject groups.

The small degree of facilitation we found to occur in the cSCI subjects we asked to 'imagine contracting/squeezing their pelvic floor, was surprising and unexpected. It is possible that this increase in PAR response may have resulted from abdominal straining. However even if subjects were straining their abdomens, PET scan studies (Blok et al, 1997) have shown that voluntary contraction of the pelvic floor is possible during activities related to abdominal straining indicating that these complete SCI subjects may have an up until now an undetected small degree of voluntary control over their pelvic sphincter (discomplete SCI) indicating the presence of residual descending pathways. Whether this facilitation is via the bulbo-spinal pathways of the GR originating in the so-called L-region or pontine storage centre (Blok, 2002) or the via the cerebro-spinal pathways (Blok et al 1997) of the GR originating in the cortex or facilitation could be through both spinal tracts, is unknown. Notwithstanding its origins this finding may indicate a potential area that might be developed therapeutically in these patients, that is currently not being taken into account by current assessment techniques such as the ASIA impairment scale.

8.5.2 *Neurophysiological Measure In Relation To ASIA/IMSOP Scale*

In this study the integrity of the GR as measured by the PARefv parameter has a significant correlation with the degree of neurological integrity as indicated by the grades of the ASIA/IMSOP impairment scale. High PARefv values were associated with subjects with higher motor scores, light touch and pin prick scores. This confirms that both the (pelvic) afferent and (pudendal) efferent limbs of the GR are involved in the maintenance of continence, the GR.

The PAR activity during voiding cystometry, indicating the extent of suppression or inhibition of the GR was found to be significantly correlation with the ASIA grades and the motor component but not the

sensory component of the ASIA/IMSOP impairment scale. It is known that classified ASIA E have very low PAR activity during voiding, and show good suppression of the EAS muscle activity which allowed unobstructed voiding. Thus the PAR response when tested during voiding cystometry has no relation to sensory scores of the ASIA, implying only the involvement of motor pathways in voiding. Voluntary voiding is dependant on sensation awareness coupled with an individual going to an appropriate place to volitionally relieve themselves. The loss of pelvic sensation is, perhaps, one of the most disabling features of spinal cord injury.

8.6 Bladder sensation

This study has looked only sporadically at the sensory element of pelvic function and aberrations in sensory function by measuring sensory function during bladder filling using the recently developed (Oliver et al, 2003) patient operated keypad device which provides a reliable objective measure of sensations of urge during urodynamics without the need for prompting from the investigator. This device was only infrequently available to the investigator, such that results were not adequate to analyse. However it was found that several of the complete SCI subjects experienced sensation described as pain, tension or burning sensation by some of the patients rather than a desire to void, toward the end of a fill. These anecdotal observations support those of Ersoz and Akyuz (2004) who also found preservation of bladder sensation in 38.9% of the patients with complete lesions above the spinal level of sensory innervation of bladder (above T11). Hypogastric nerve (T11-L2) is the most proximal sensory innervation of bladder with respect to spinal level. For the lower urinary tract, the effect of a complete spinal cord lesion is to block ascending afferent activity from the bladder or urethra reaching the brain-stem peri-aquaductal gray during filling and prevent proper pontine coordination of the bladder and

sphincters. In fact, all sensations from the lower urinary tract, bowel, pelvic floor and sphincters would be absent as a result of such a lesion and this would include other proprioceptive pathways normally linking the pelvic floor more directly with the somato-sensory cortex. Ersoz and Akyuz (2004) explained the preserved bladder-filling sensation in patients with complete lesions above T11 by the assumption that some neurological tracts in the spinal cord that carry bladder-filling sensation and are different from the ones that carry pinprick and light touch sensations may be spared in SCI patients.

8.7 Relation Of The Somatovisceral Measure With The Guarding Response

By combining the somatic pudendo-anal reflex measurement with urodynamics we have demonstrated facilitatory effects of the pelvic afferent activity from the bladder on the sphincters. The modulation of the PAR increased at end fill volume in non-SCI subjects and was suppressed during bladder emptying. This increase at end fill volume was obviously associated with a high integrity GR which maintained continence, by preventing leaking.

We have confirmed previous findings using needle EMG (Siroky and Kane, 1982) that at bladder end fill the GR, was absent or very weak in most subjects classified with a neurologically defined complete supra-sacral spinal cord lesion (ASIA A). In subjects classified with incomplete lesions (ASIA B-D), the GR was often preserved but very variable. The GR appears to require involvement of the M-region as well as the integrity of supra-sacral pathways. Interestingly, recent neurophysiological testing of the pathways of a similar reflex (bladder-anal) has revealed a long latency of around 90 milliseconds (Basinski et al, 2003) suggesting that the GR probably involves many interneurones in its arc even engaging a supra-spinal pathway (Park et al, 1997). Accumulating evidence indicates the

presence of a variety of interneuron populations in the sacral circuitry participating in the coordination of activity in parasympathetic bladder efferents with that of the striated urethral sphincter motorneurones (Shefchyk 2001). Following injury to descending excitatory modulating influences from the L-region to Onuf's nucleus in the sacral cord we would expect poor or absent sphincter GR and the loss of reflex inhibition of detrusor activity during the filling phase (Park et al, 1997). A weak GR is often associated with low bladder capacity that may be a result of weak pudendal inhibition of aberrant detrusor contractions. Here we have bladder volumes to be related to neurological integrity.

It has recently been discovered that whilst an analogous bowel "guarding response" during rectal filling exists it appears to be present irrespective of spinal cord injury (Chung et al, 2004) therefore showing no significant correlation with completeness of lesion unlike the bladder guarding response. Perhaps this is a reflection of the greater dependence on automatic control in bowel function; the guarding response requiring only sacral segmental control.

8.8 Relation Of The Somatovisceral Measure With The Suppression of the Guarding Response

This kinesiological measure of the evoked PAR response with bladder function was found to reflect the GR and its varying degrees of pelvic dysfunction manifested in those with SCI, presenting itself as a reliable and robust somatovisceral tool.

8.8.1 *Non-Spinal Injured Subjects*

The PAR in non-SCI subjects was suppressed during bladder emptying. During voiding the inhibition or suppression of PAR activity reflected the GR being switched off to allow unobstructed voiding. These findings

confirmed those of Dyro and Yalla (1986) and correlated well with the standard electromyographic findings seen with filling and voiding cystometrograms. Sethi et al (1989) found that only 90% of non-SCI subjects had no BCR during voiding, we found suppression of the PARvoid in 100% of our non-SCI subjects. This discrepancy may have been caused by a variety of reasons. Sethi et al. (1989) used needle EMG, eliciting the BCR by compression of the glans penis, which was a subjective elicitation of the sacral reflex, whereas there was no doubt as to whether the DPN elicited the PAR response. It may be that the small sample size of our non-SCI population gave very slanted data, or just that 10% of their subjects felt too inhibited to micturate in laboratory conditions.

8.8.2 *Spinal Cord Injured Subjects*

In the SCI subjects there were varying degrees of suppression of PAR activity during voiding/NDO, clearly indicated by the large standard deviations. Subjects known to experience detrusor sphincter dyssynergia (DSD) as per their hospital urodynamics reports had an exaggerated PAR response. This was found more so in the cSCI subjects supporting previous findings (Dyro and Yalla, 1986; Sethi et al, 1989). The loss of suprasegmental inhibition of sacral reflexes during voiding has been shown to be a more sensitive indicator of UMN lesions, but a slightly less specific indicator than DSD (Sethi et al 1989). The PAR response tested during voiding was also found to be affected by level of the lesion, those with cervical lesion appearing to have less PAR activity during periods of NDO than those with thoracic lesions in iSCI subjects.

It was found that during periods of NDO the amount of fluid leaked by subjects was related to the level of PAR activity- this ties demonstrates that the GR is reflected in the level of PAR activity, even during dysfunctional voiding when an increased PAR activity, is manifest by no

leaking, or very minimal leaking/firing off. This data may be skewed because of the inclusion of subjects known to have DSD, perhaps a future study could incorporate a cohort of SCI subject known only to experience NDO with no accompanying DSD, to evaluate the range of $PAR_{void/NDO}$ data.

If activation of the M-region was dysfunctional then the drive necessary for bladder emptying would also be missing. A combination of these effects and the loss of voluntary descending control of the sphincters and facilitation of the guarding reflex could be to disinhibit visceral A...afferent activity allowing sacral hyperreflexia to predominate, reducing bladder capacity. In addition, the loss of any descending pathways from the brain stem, normally keeping reflexes mediated by bladder C-fiber afferents in check, could also make the bladder more sensitive to distension, again tending to drive the bladder towards overactivity and lower capacity (Yoshimura, 1999, de Groat and Yoshimura (2005)). The exact mechanism of C-fiber hyper-excitability is not entirely clear after SCI. It could be due to a change in the mechanical sensitivity of the sensory endings, but more likely it involves reorganization in the spinal neural circuitry (Shefchyk, 2002). Perhaps there is proliferation of sacral spinal connections of these afferent pathways, brought about by new occupation of vacant excitatory post-synaptic receptor sites in the sacral segmental pelvic reflex pathway. The vacancy might follow degeneration of the excitatory pathway from the M-region, which under normal bladder filling conditions would be silent but comes into play to activate the detrusor for voiding. Speculatively, these receptor sites in the sacral cord could be taken over by collateral sprouting of the bladder afferents. That DSD is due to an inability to inhibit sphincter activity due to a loss or disruption, following injury, to descending pathways (Shefchyk (2006), probably from the M-region of the pons, highlights the target for potential neural repair.

8.9 Modulation By Transcranial Magnetic Stimulation

The findings presented in this study demonstrate in the main and for both the non-SCI and the ASIA D incomplete subjects that the descending pathways are excitatory, as indicated by the facilitation of the evoked PAR response that results from a conditioning/advanced TMS pulse. Based on the finding that suppression of the PAR response is found when the TMS pulse follows the DPN stimulation, intimates that inhibition occurs at a segmental level. Unsurprisingly the facilitation of the PAR response was much greater in the non-SCI subjects than in the iSCI subjects although the time course of facilitation was similar.

It's known that movement planning occurs in the spinal cord in the absence of muscle activity. During this instructed delay period about one-third of the interneurons show modulation of resting activity, a few of these interneurons increase their firing rate during delay and then show a further increase during the time of movement as if they had a priming function for the motor neurons. Most modulated interneurons are inhibited during the delay period and so suppress the tendency to initiate movements. The excitatory and inhibitory activity that is shown by this time domain TMS study may reflect possible modulation of interneurons during voluntary contraction of the pelvic floor. Further experiments are now being conducted to identify the site(s) of interaction of these pathways and to determine whether the aberrant neural mechanisms in SCI might be responsive to repetitive TMS by tapping into neural plasticity for restoring normal facilitatory function. Thus such condition-testing will be useful for assessing the efficacy of any technique aimed at restoring normal function of the bladder and sphincter function in SCI.

8.10 Uncontrolled (/Uncontrollable) Variables

In some of the SCI subjects no PAR was monitored during voiding cystometry even though their urological reports indicated the presence of NDO. There was variety of known reasons for this such as in some subjects discomfort was experienced at which time the study was halted; or because normal void on urge was inhibited in the subject by the artificial laboratory surroundings. However in some cases the subject appeared to have a flaccid acontractile bladder, a loss in bladder compliance which was in some cases accompanied by no sensation or discomfort during bladder filling and no NDO. It was discovered than some subjects were taking medication or recreational drugs as pain relief (emotional and/physical). This type of self-medicating is very much a part of the human condition. Some types of compounds prescribed (e.g. baclofen) or self-prescribed (e.g. cannabis) which are known to increase the compliance of the bladder. Also urological management reflects the manifestation of pelvic dysfunction, in bladder capacity and perhaps also the range of values for the PAR responses. In light of this it is very important to take a very canny history of the subject before experimentation which would aid the interpretation of the results in explaining the variability which occurs. And perhaps categorising the PAR responses according to management in a larger sample size would give more information as to the effects of urological management on pelvic function.

8.11 Future Studies

It has been known for a long time that electrical stimulation of pudendal nerves can have a beneficial effect on the lower urinary tract (Vereecken *et al* 1984). This is known as *neuromodulation* (NM), where the 'influence of activity in one neural pathway modulates the pre-existing activity in another through synaptic interaction' (Craggs and McFarlane 1999).

Various papers have shown that DPN stimulation causes the suppression of NDO (Vodusek *et al* 1986; Kondo *et al* 1982; Shah *et al* 1998; Kirkham *et al* 2001) leading to an increase in bladder capacity (BC) in SCI subjects. It is unknown whether NM in SCI subjects alters the GR. It would be interesting to assess whether with increasing bladder volumes there is an increase or a stasis of the GR. If the GR is increased with the increased BC it may be that after a SCI there is a reorganisation in the spinal cord, which results in a GR at a segmental level, which can alter with the BC change. Another technique to test this theory could be to use anti-cholinergics (Wein, 2001) to increase the bladder capacity in these SCI subjects and to monitor again any changes in the PAR response. Preliminary work so far has found great variability in the behaviour of the GR with NM. It is known that NM does not increase bladder capacity in all subjects, as it was found in an ASIA D subject, however, NM was found to facilitate the same subjects PARefv. This NM study has also been performed on two cSCI subjects, in one it was found to increase both PARefv and BC, and in the second it was found to only increase BC. These differing results perhaps reflect the substantial variations that exist in spinal cord injury (level and extent).

Preliminary work has also been done in a non-SCI subject to assess the effect of maximal volitional contraction of the pelvic floor and sphincters at different bladder volumes. Findings show that voluntary contraction sustained the normalised PAR response at 2.0-2.5 from the start filling cystometry to 57% bladder capacity, after which the subject was only able to facilitate the normalised PAR response to 1.6, with maximal bladder capacity being 700 ml.

The exciting concepts of neural regeneration and repair may one day provide full restoration of function in SCI. However, for the current

generation of patients with long-standing spinal lesions, in the absence of techniques applicable to humans at this time (National Institute for Neurological Disorders and Stroke), other methods using Pelvic Floor Muscle Training (PFMT) of residual voluntary spinal pathways could provide a practical therapy for the foreseeable future. Furthermore, such a technique might also be facilitatory for restoring neural connectivity when spinal repair does eventually become a reality.

8.12 Impact Of Study Finding On The Problem Of Bladder Sphincter Coordination

Routine assessment of patients with SCI currently relies on subjective clinical measurement using the ASIA classification and Impairment Score. It is not always consistently rated and neither does it assess autonomic function. Although recent somato-sensory (Krassioukov et al, 1999) and somato-motor (Smith et al, 2000) testing is introducing more objective neurophysiological measures into the evaluation of people with incomplete spinal cord injury, their sensitivity is not indicated. Any ephemeral changes in nerve pathways that might be brought about by new interventional therapies might be picked up by the somatovisceral measure technique presented in this thesis, using the reflex activity in the EAS with bladder function, as a measure of the GR. Supporting this endeavor is recent research (Wenzel et al. 2006) confirming that recordings of the EAS EMG can be used to detect robustly the onset of neurogenic detrusor contraction. Figure 8.0 illustrates degrees of the different bladder sphincter degrees of coordination/synergy within the pelvic functional and dysfunctional arena of the somatovisceral measure, reflecting the GR and also including the volitional aspect of the GR.

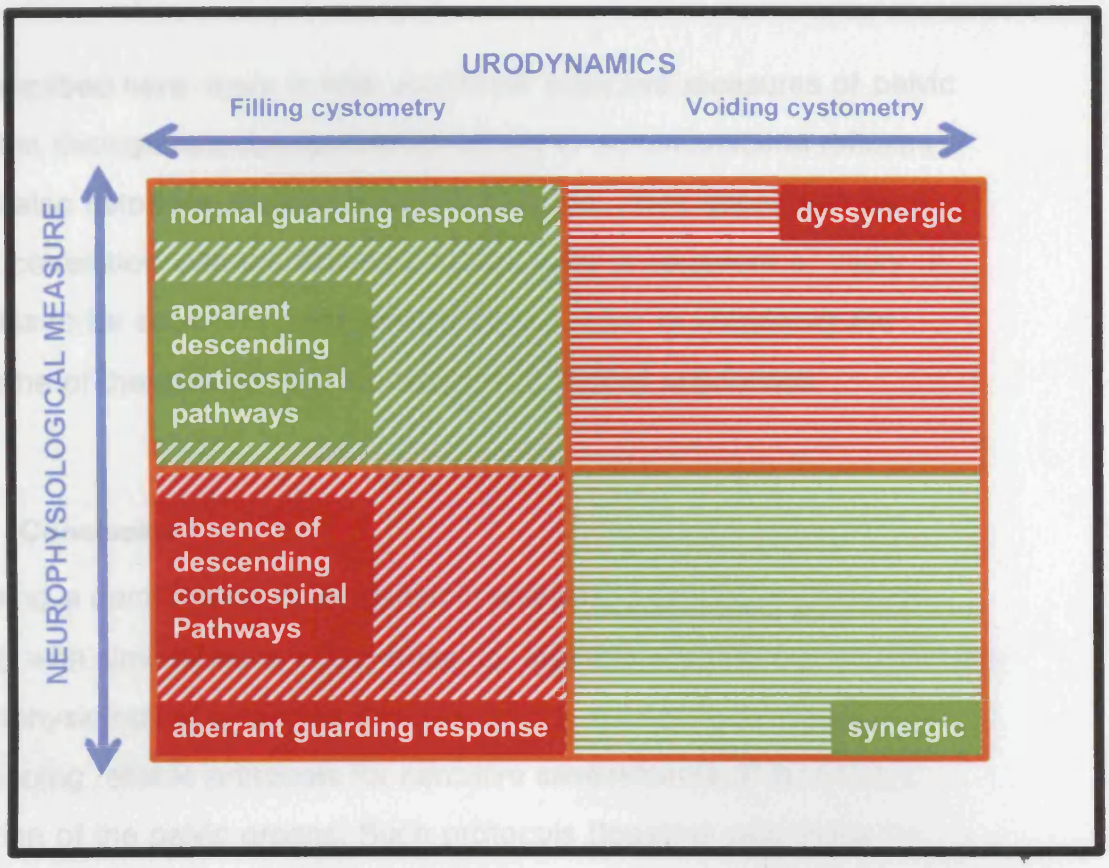


Figure 8.0 The Somatovisceral Measure

The somatovisceral measure resulting from the testing of the neurophysiological testing of the PAR response (y-axis) with urodynamics procedures (x-axis)

Good function is depicted in green and dysfunction in red.

Diagonal hatches: filling cystometry, PARefv
The green indicates a guarding response where PARefv > 1. The subdivision block indicates ability to faciliate the PAR response with volitional effort: PARvc > 1, signifying the presence of descending pathways.

The red block indicates absence of the guarding response where PARefv < 1. The subdivision block signifying no residual descending pathways (PARvc < 1).

Horizontal hatches: voiding cystometry, $PAR_{void/NDO}$
The green block indicate the good bladder sphincter coordination where PARvoid/NDO < 1 signifying unobstructed voiding. The red block indicates pronounced dyssynergic bladder sphincter behaviour where PARvoid/NDO > 1.

As described here, there is little doubt that objective measures of pelvic function through neurophysiological testing of somatovisceral reflexes could also help to evaluate autonomic function; there appears to be a good correlation with the standard neurological assessment of injury. It remains to be seen how sensitive the tests will be for assessing the outcome of therapeutic interventions for functional restoration.

8.13 Conclusion

By using a combination of urodynamic and proctodynamic techniques, ideally with simultaneous video-imaging, together with the sort of objective neurophysiological measures described here, we can look forward to developing reliable protocols for sensitive assessments of autonomic function of the pelvic organs. Such protocols (together with those for assessing other autonomic physiological disturbances in spinal cord injury) will help us to characterize all autonomic dysfunction more objectively. These can then be combined with the other well-established neurological and neurophysiological assessments to give a much more comprehensive picture of spinal cord injury and the effect of interventions. The ultimate goal for all those concerned with autonomic function of the bladder and bowel will be to develop a robust impairment grading and scoring system for pelvic dysfunction.

Repairing the long spinal pathways to and from the brain stem and cortex will be an important step towards functional restoration of the lower urinary tract in spinal cord injury. Figure 8.1 show speculative potential sites, 1-4, for neural repair.

Site 1 Spinal injury resulting in a loss of descending excitatory modulating influences to Onuf's nucleus would lead to the patient presenting with a poor or absent guarding response (GR) and a loss of reflex inhibition of detrusor activity during the filling phase.

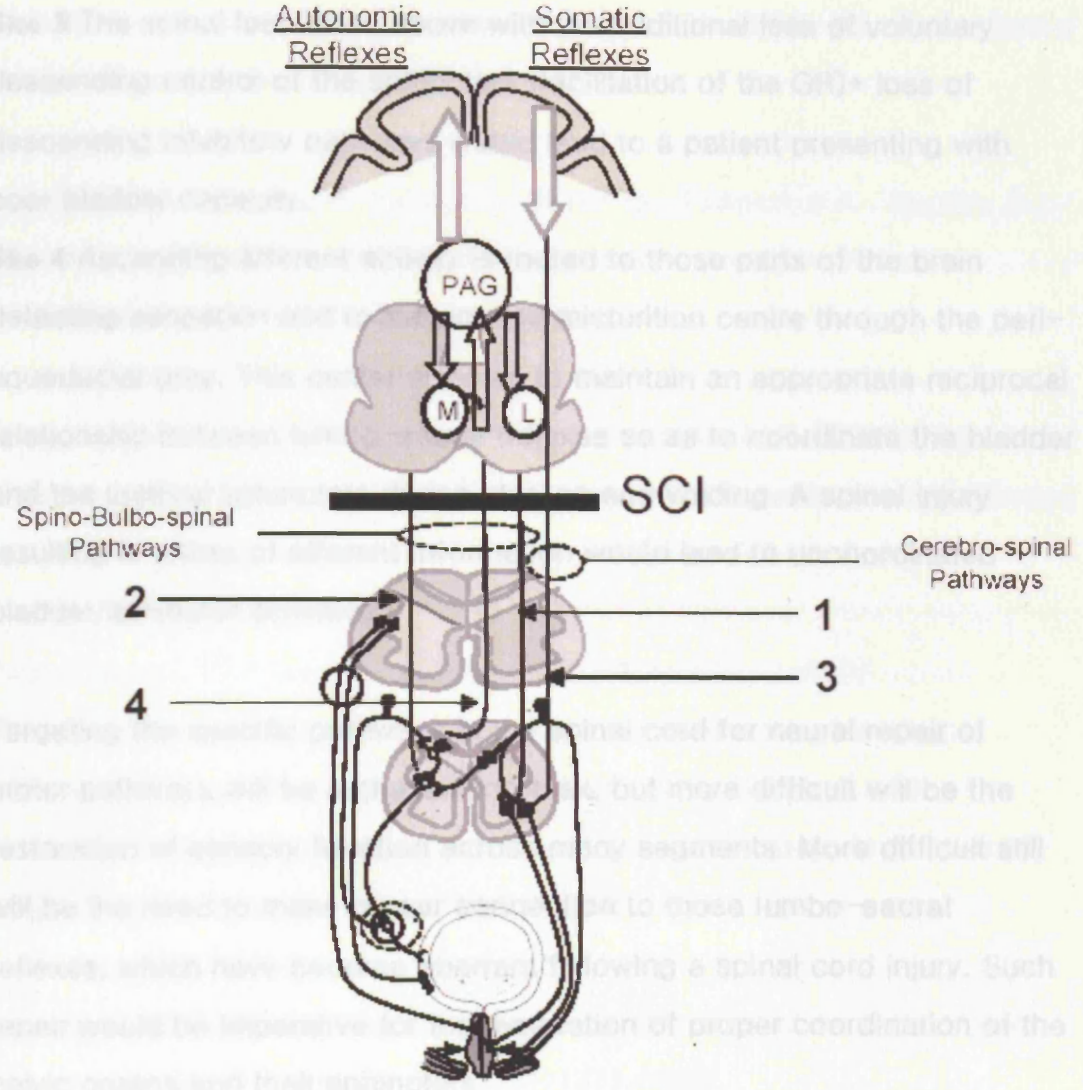


Figure 8.1 Possible Sites For Neural Repair To Restore Lower Urinary Tract

Site 2 Spinal injury resulting in a loss of drive to the pontine micturition centre (M) would lead to a patient presenting with impaired bladder emptying.

Site 3 The spinal loss listed above with the additional loss of voluntary descending control of the sphincters (facilitation of the GR)+ loss of descending inhibitory pathways would lead to a patient presenting with poor bladder capacity.

Site 4 Ascending afferent activity is routed to those parts of the brain detecting sensation and to the pontine micturition centre through the peri-aqueductal gray. This center appears to maintain an appropriate reciprocal relationship between lumbo-sacral reflexes so as to coordinate the bladder and the urethral sphincters during storage and voiding. A spinal injury resulting in a loss of afferent information would lead to uncoordinated bladder/sphincter activities.

Targeting the specific pathways in the spinal cord for neural repair of motor pathways will be a challenging task, but more difficult will be the restoration of sensory function across many segments. More difficult still will be the need to make proper connection to those lumbo-sacral reflexes, which have become aberrant following a spinal cord injury. Such repair would be imperative for the restoration of proper coordination of the pelvic organs and their sphincters.

Perhaps a better approach for the future would be to study the processes that change in the sacral spinal cord during the so-called spinal shock phase of recovery (Wrathall and Emch, 2006) and develop strategies to prevent the emergence of aberrant reflexes in the hope that we can improve the chances of proper reconnection with restored supra-sacral pathways.

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ASIA E	LATENCY OF PAR	H01	H02	H03	H04	H05
absolute	empty	27	27	28	24	32
	efv	27.5	27.5	34.5	26	32
	void/ndo	30	30.5	31	24	35
normalised	empty	1	1	1	1	1
	efv	1.018	1.018	1.232	1.083	1
	void/ndo	1.111	1.129	1.107	1	1.093

ASIA D	LATENCY OF PAR	P07: normal/T2	P16: C5/C6	P20: T1/T9	P22: C5/T3	P26: C4/C3
absolute	empty	21	26	29	25.5	23.5
	efv	20.5	26.5	27.5	30.5	26
	void/ndo	23.5	25	28	36	
normalised	empty	1	1	1	1	1
	efv	0.976	1.019	0.948	1.196	1.106
	void/ndo	1.119	0.961	0.965	1.411	

ASIA C	LATENCY OF PAR	P13: C5/T7	P14: T1/T9	P19: C7/C8	P23: C6/T4
absolute	empty	32	22	27.5	32
	efv	28	27	28	35.5
	void/ndo	30		30	
normalised	empty	1	1	1	1
	efv	0.875	1.227	1.018	1.109
	void/ndo	0.937		1.090	

ASIA B	LATENCY OF PAR	P01: T1/T9	P04: C5/T7	P05: T1/T9	P08: T1/T10	P18: C8/C7
absolute	empty	21	24.5	27.5	31	37
	efv	21	26.5	27.5	33.5	35
	void/ndo		26	27.5	31	36
normalised	empty	1	1	1	1	1
	efv	1	1.081	1	1.080	0.945
	void/ndo		1.061	1	1	0.972

ASIA A	LATENCY OF PAR	P9: T1/T7(T8-T11sens)	P10:T1/T6 (T7-T11sens)	P12 T1/T5 (T6-T8sens)	P15: T1/T5 (T5sen)	P17:T1/T5 (T5sens)
absolute	empty	23	27	34	28	33
	efv	25.5	34.5	27.5	30	37
	void/ndo			33.5	29	25.5
normalised	empty	1	1	1	1	1
	efv	1.108	1.277	0.808	1.071	1.121
	void/ndo			0.985	1.035	0.772

ASIA A	LATENCY OF PAR	P25: T1/T4(T5sens)	P03: T1/T8	P06: none/C4	P11: T1/T5	P21: C5/C4
absolute	empty	30	45.5	28.5	28.5	28
	efv	35	39	27	23.5	27.5
	void/ndo	35		29	32	28.5
normalised	empty	1	1	1	1	1
	efv	1.166	0.857	0.947	0.824	0.982
	void/ndo	1.166		1.017	1.122	1.017

Appendix 1

ASIA E	PAR	H01	H02	H03	H04	H05
absolute	empty	0.139	0.025	0.028	0.031	0.033
	efv	0.190	0.038	0.032	0.043	0.052
	void/ndo	0.048	0.017	0.004	0.011	0.005
normalised	empty	1	1	1	1	1
	efv	1.376	1.538	1.164	1.402	1.585
	void/ndo	0.351	0.692	0.149	0.369	0.168

ASIA D	PAR	P07: normal/T2	P16: C5/C6	P20: T1/T9	P22: C5/T3	P26: C4/C3
absolute	empty	0.037	0.033	0.004	0.013	0.069
	efv	0.059	0.037	0.005	0.023	0.060
	void/ndo	0.086	0.006	0.008	0.023	
normalised	empty	1	1	1	1	1
	efv	1.61	1.14	1.43	1.79	0.87
	void/ndo	1.45	0.16	1.5	1.01	

ASIA C	PAR	P13: C5/T7	P14: T1/T9	P19: C7/C8	P23: C6/T4
absolute	empty	0.006	0.046	0.022	0.011
	efv	0.007	0.048	0.017	0.015
	void/ndo	0.014		0.008	
normalised	empty	1	1	1	1
	efv	1.21	1.06	0.81	1.39
	void/ndo	1.96		0.47	

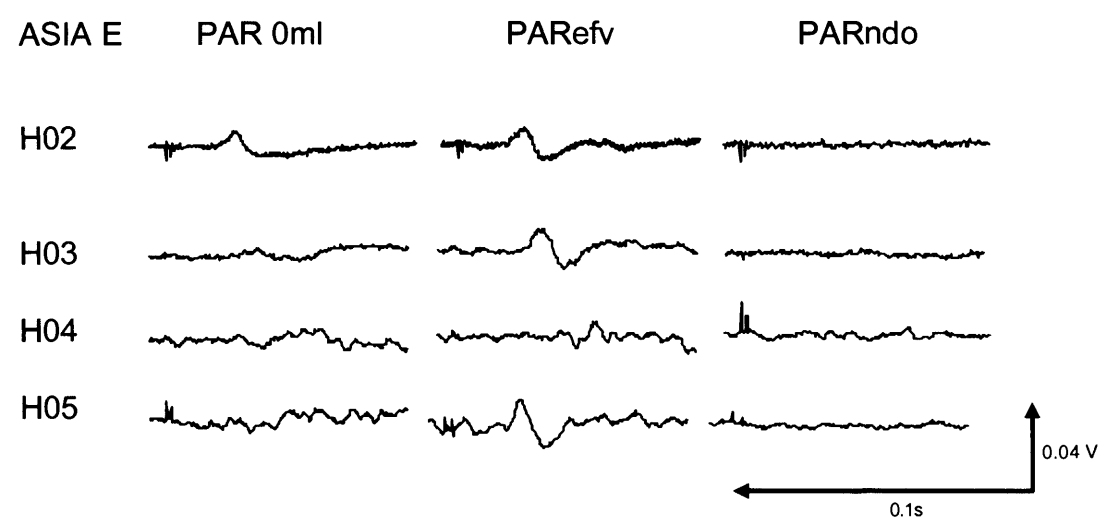
ASIA B	PAR	P01: T1/T9	P04: C5/T7	P05: T1/T9	P08: T1/T10	P18: C8/C7
absolute	empty	0.055	0.074	0.086	0.030	0.018
	efv	0.083	0.044	0.071	0.046	0.021
	void/ndo		0.008	0.149	0.054	0.015
normalised	empty	1	1	1	1	1
	efv	1.51	0.6	0.83	1.51	1.18
	void/ndo		0.2	2.1	1.18	0.72

ASIA A	PAR	P9: T1/T7(T8-T11sens)	P10:T1/T6 (T7-T11sens)	P12 T1/T5 (T6-T8sens)	P15: T1/T5 (T5sen)	P17:T1/T5 (T5sens)
absolute	empty	0.014	0.028	0.012	0.012	0.01
	efv	0.015	0.025	0.010	0.029	0.011
	void/ndo	0.01554	0.044307	0.013683	0	0.006667
normalised	empty	1	1	1	1	1
	efv	1.11	0.92	0.873	2.48	1.13
	void/ndo	1	1.72	1.305		0.59

ASIA A	PAR	P25: T1/T4(T5sens)	P03: T1/T8	P06: none/C4	P11: T1/T5	P21: C5/C4
absolute	empty	0.03	0.03	0.082	0.03	0.043
	efv	0.026	0.044	0.054	0.016	0.043
	void/ndo	0.014	0	0	0.025	0.034
normalised	empty	1	1	1	1	1
	efv	0.89	1.48	0.66	0.562	1.01
	void/ndo	0.56			1.53	0.79

Appendix 2

Appendix 3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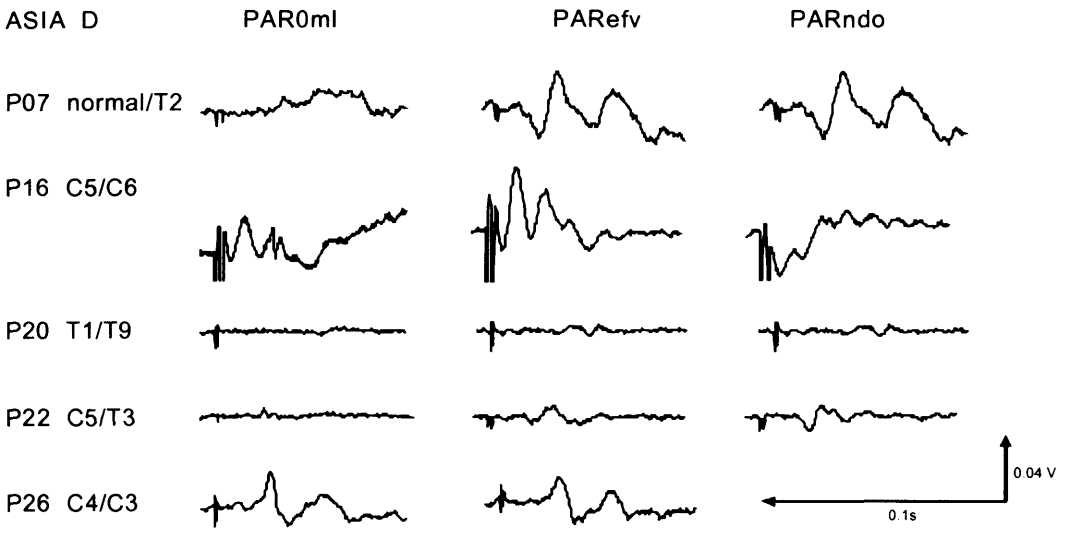
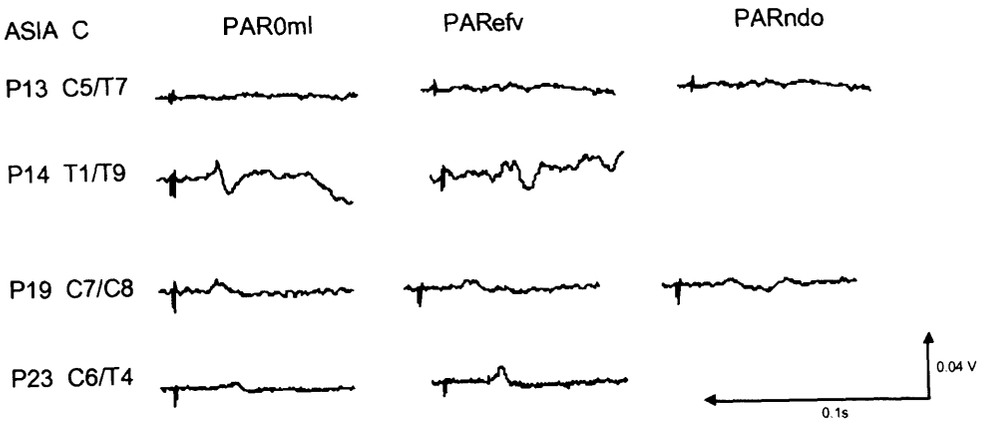
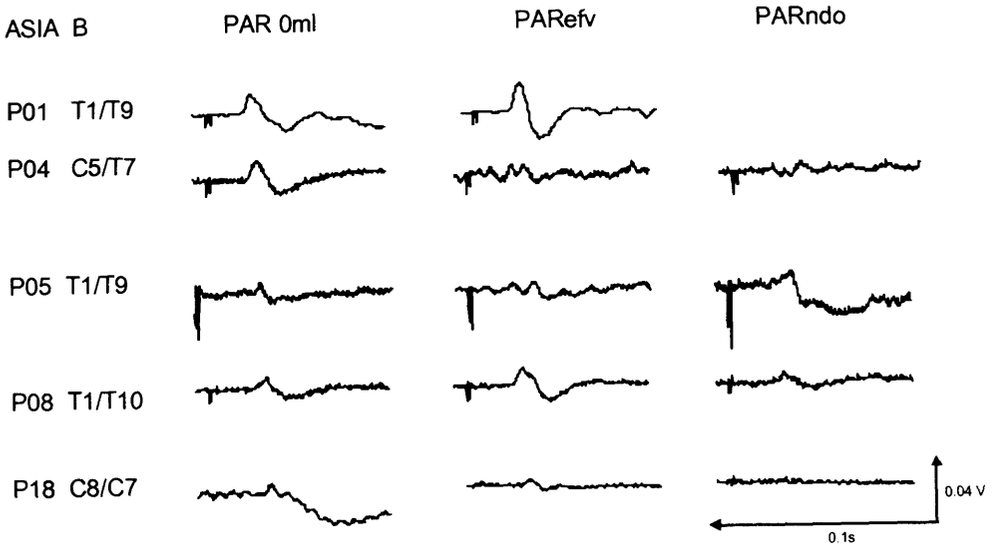
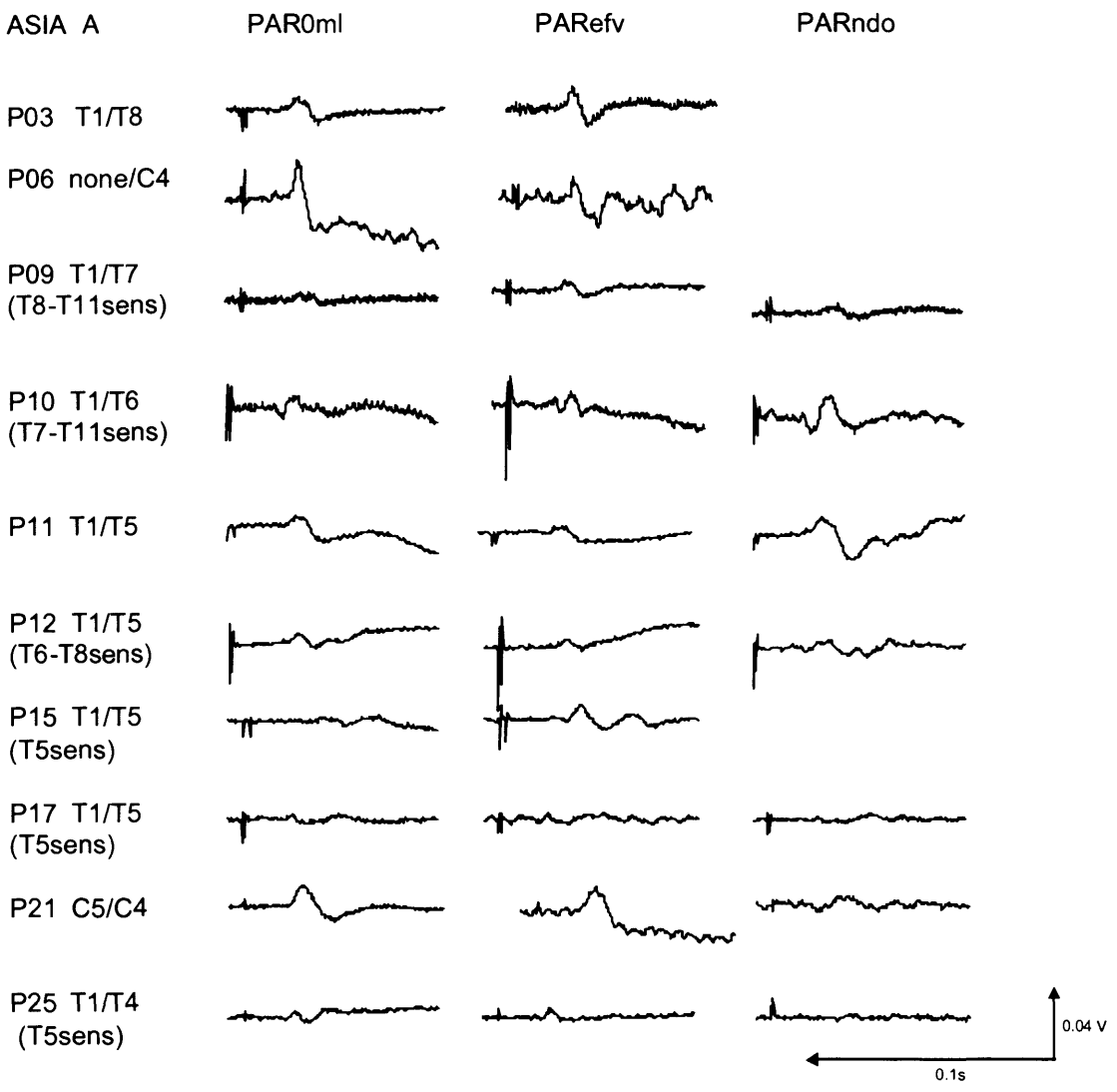
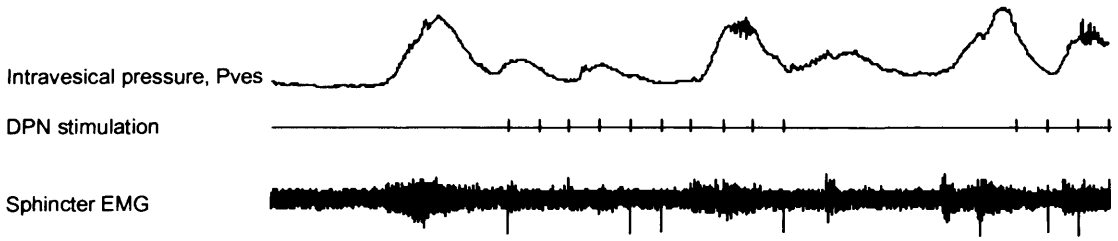
PAR 0ml
PARefv
PARndo
H02
H03
H04
H05
0.04 V
0.1s


ASIA D
PAR0ml
PARefv
PARndo
P07 normal/T2
P16 C5/C6
P20 T1/T9
P22 C5/T3
P26 C4/C3
0.04 V
0.1s


ASIA C
PAR0ml
PARefv
PARndo
P13 C5/T7
P14 T1/T9
P19 C7/C8
P23 C6/T4
0.04 V
0.1s

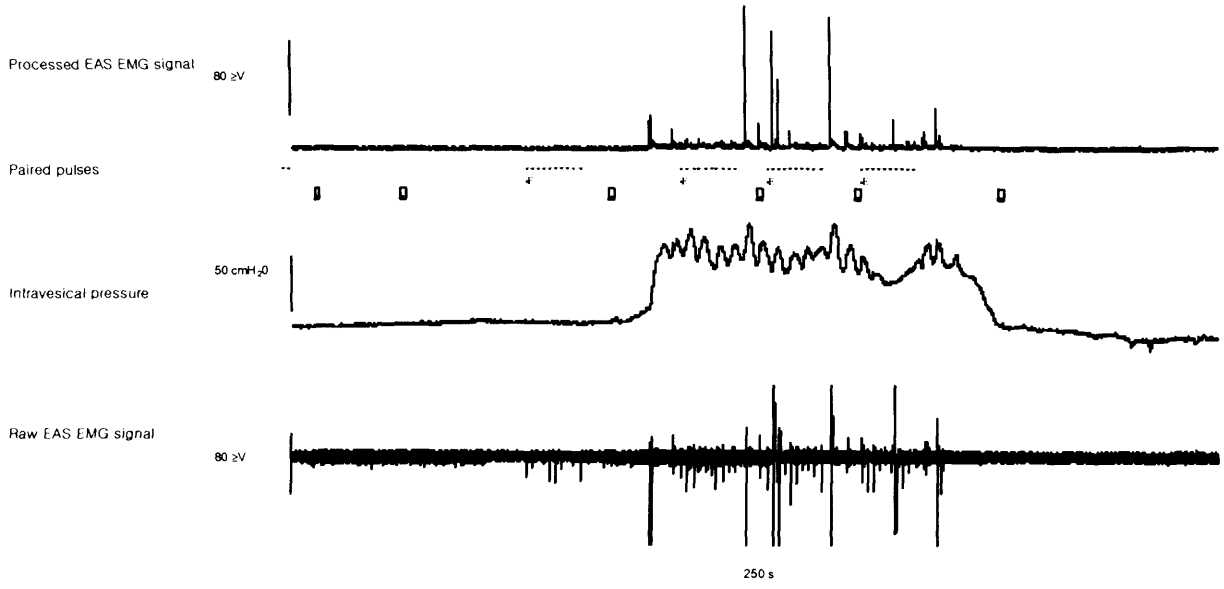

ASIA B
PAR 0ml
PARefv
PARndo
P01 T1/T9
P04 C5/T7
P05 T1/T9
P08 T1/T10
P18 C8/C7
0.04 V
0.1s


ASIA A
PAR0ml
PARefv
PARndo
P03 T1/T8
P06 none/C4
P09 T1/T7
(T8-T11sens)
P10 T1/T6
(T7-T11sens)
P11 T1/T5
P12 T1/T5
(T6-T8sens)
P15 T1/T5
(T5sens)
P17 T1/T5
(T5sens)
P21 C5/C4
P25 T1/T4
(T5sens)
0.04 V
0.1s



Appendix 4 Example Of Detrusor Sphincter Dyssynergia In Isci Subject P20

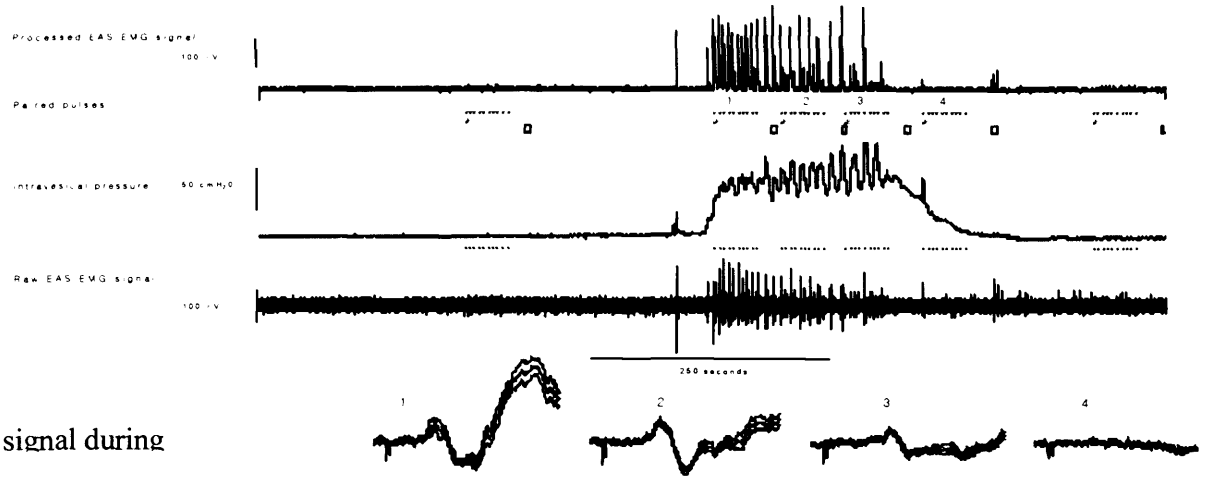
The traces shown here are from results taken during voiding cystometry in subject P20 (T1/T9) classified as grade ASIA D. For this subject $PAR_{void/NO}$=1.5 during which Pves rose to 50 cmH2O. Dyssynergia is clearly depicted by the intravesical pressure rises that coincide with the episodes of increased sphincter EMG activity.



Appendix 5 **Example of triple PAR sampling during a period of NDO in an incomplete SCI subject (P05)**

The top trace shows the processed EAS EMG signal post digital processing of the raw EAS EMG signal showed in the bottom trace. The middle trace shows the intravesical pressure (Pves), which was used to predict NDO.

PARndo 1.4
PARndo 0.85

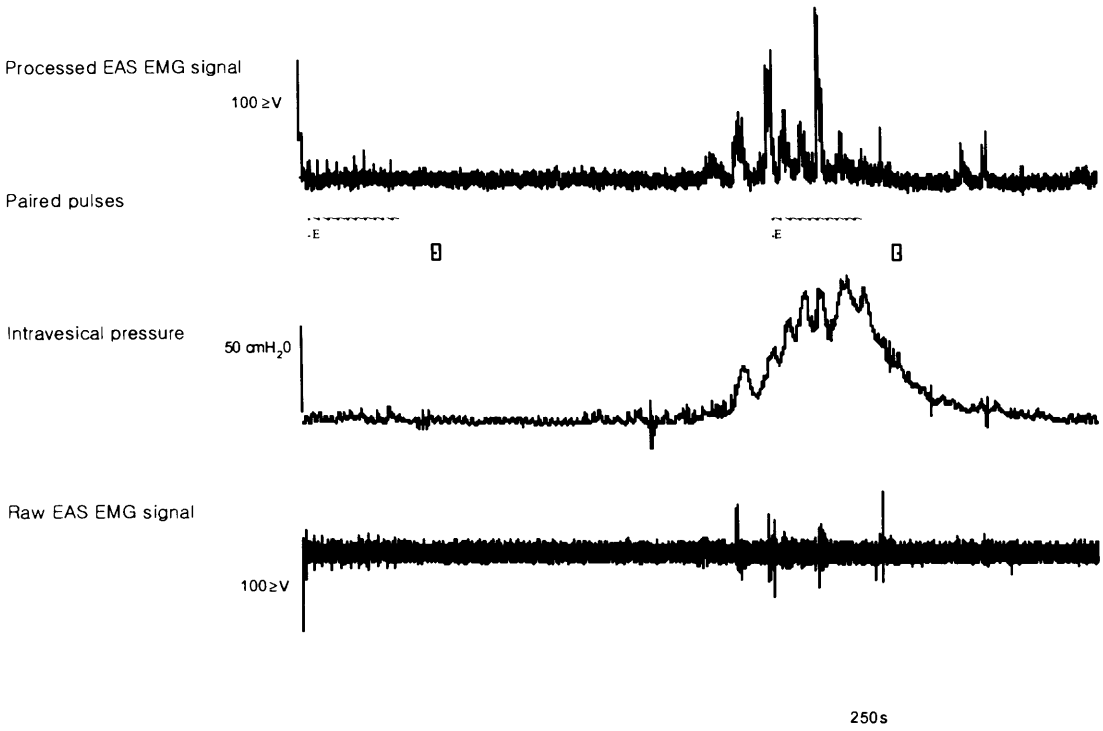


Averaged PAR signal during

Appendix 6 **Example of PAR sampling during a period of NDO in a complete SCI subject (P11)**

The top trace shows the processed EAS EMG signal post digital processing of the raw EAS EMG signal showed in the third trace, the second trace shows the intravesical pressure with the DPN markers and .at the bottom are their resulting averaged PAR traces.

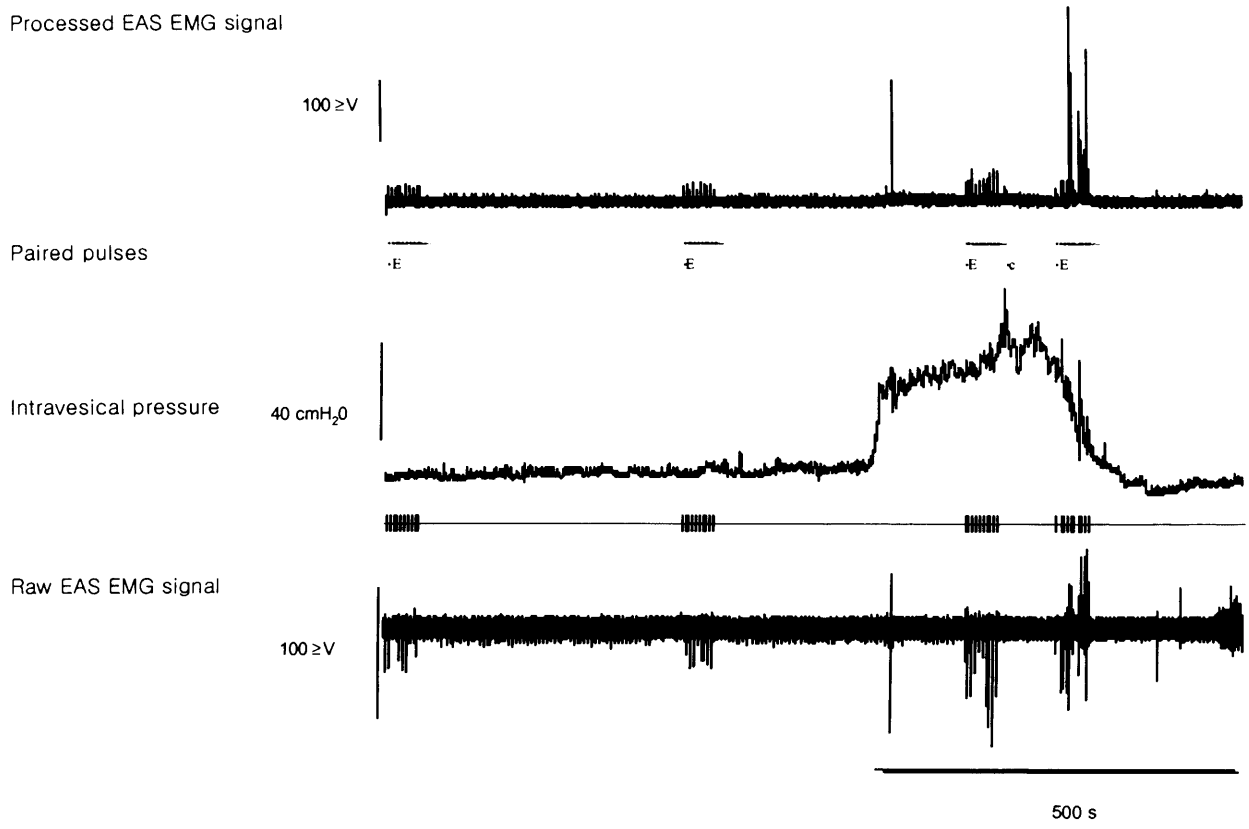
PARndo1	1.53
PARndo2	2.60
PARndo3	0.58
PARempty	0.19



Appendix 7 **Example of a singular PAR sampling during a period of ndo in a complete SCI subject (P21)**

The top trace shows the processed EAS EMG signal post digital processing of the raw EAS EMG signal showed in the bottom trace. The middle trace shows the Pves, which was used to predict NDO.

PARndo 0.79.

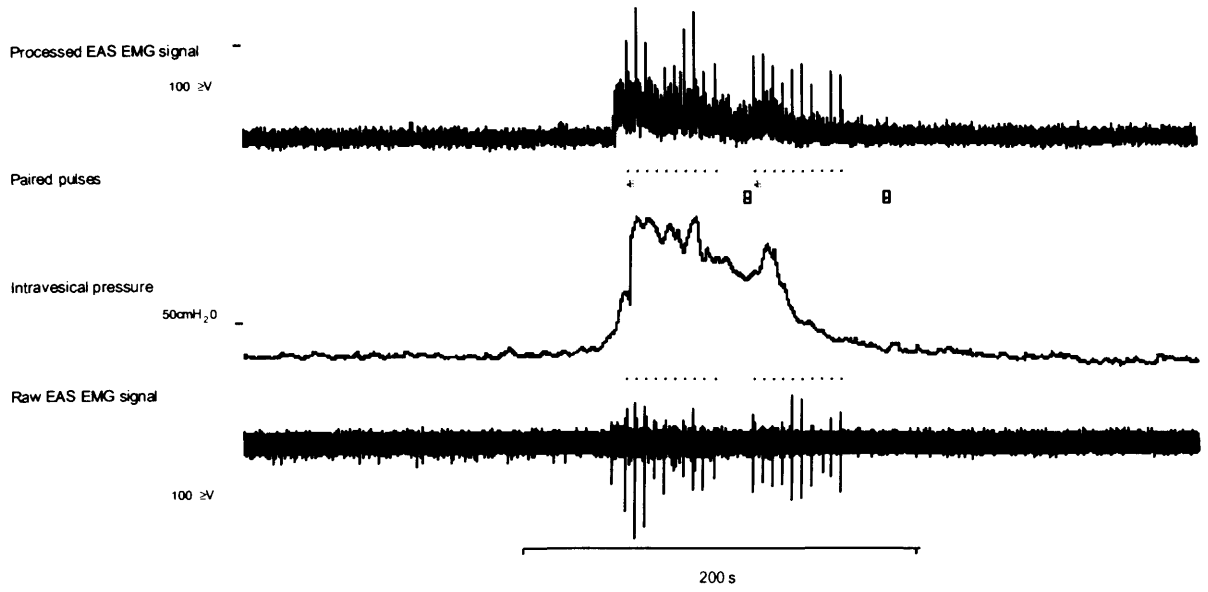


Appendix 8 **Example of double PAR sampling during a period of ndo in a complete SCI subject (P10)**

The top trace shows the processed EAS EMG signal post digital processing of the raw EAS EMG signal showed in the bottom trace. The middle trace shows the Pves, which was used to predict NDO.

PARndo 1.00

PARndo 1.60



Appendix 9 **Example of PAR sampling during a period of ndo in a complete SCI subject (P12)**

The top trace shows the processed EAS EMG signal post digital processing of the raw EAS EMG signal showed in the bottom trace, the middle trace shows the intravesical pressure with the DPN markers.

PARndo	1.38
PARndo	1.15

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CONSENT FORM

Agreement to participate in a clinical investigation

Investigators: Professor MD Craggs, Director of Spinal Research
Dr FRI Middleton FRCP, Consultant Rehabilitation Physician
Professor Clare Fowler, Consultant Uro-Neurologist

Mr PJR Shah FRCS, Consultant Urological Surgeon
Mr J Bycroft MRCS, Clinical Research Fellow, Urologist
Mr AE Chung MRCS, Clinical Research Fellow, Proctologist
Dr SL Knight, Hon Senior Clinical Scientist
Ms AV Balasubramaniam Mphil, MSc, BSc (Hons.), Research Fellow

1. I have read the information sheet concerning this study and I understand what will be required of me if I take part in this study.
2. My concerns regarding this study have been answered by .....
3. I understand that at any time I may withdraw from this study without giving a reason and without affecting my normal care and management.
4. I understand that the information from this study may be published in scientific journals, but that I will not be identified.
5. I agree to take part in this study.

Patient's signature or independent witness.....

Name in BLOCK LETTERS .....

Date .....

Doctor's signature .....

Name in BLOCK LETTERS .....

Date .....

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A NEURO-PHYSIOLOGICAL AND URODYNAMIC ASSESSMENT OF RESIDUAL SUPRA-SACRAL SENSORY-MOTOR PATHWAYS AND THEIR INFLUENCE ON ABERRANT SACRAL REFLEXES IN SPINAL CORD INJURY

PATIENT INFORMATION SHEET

You have been invited to participate in this clinical investigation because you have a spinal injury, which has led to some bladder and bowel dysfunction. The aim of this study is to develop a full neurophysiological assessment programme of residual bladder, bowel and sphincter function, which would help patients with spinal cord damage in the following ways:

- provide a tool for assessing and optimising the outcome of future nerve regeneration techniques
- improve our understanding of recovery of bladder function in spinal cord injured patients which will benefit the development of future nerve regeneration techniques. This will contribute to improve bladder management and treatment options.

The Royal National Orthopaedic Hospital Trust Joint Research and Ethics Committee has given approval for this work.

The investigation involves the monitoring of the sacral nerve reflexes. These involve the nerves that come from the bottom of your spinal cord and supply the bladder, bowel and sphincters of the pelvic floor.

This can be achieved by the following investigation techniques:

- We will place two surface stimulating devices onto the base of the penis/clitoris. Through which we will pass a small electrical current. This internationally used technique is called *Dorsal Penile (/Clitoral) Nerve Stimulation*. We have perfected it and used it in many other research projects and it is painless.
- A small monitoring device is placed into the anus to measure the activity in the anal sphincter to measure the pudeno-anal reflex (the nerve reflex

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- Two small flexible tubes (microtip pressure transducers) will be placed into your urethra (urine pipe) and your rectum to measure urethral and rectal pressures respectively.
- During a subsequent visit we may also measure the electrical activity in the urethral sphincter using a needle-monitoring device. (This will not be done during the initial visit but may be done on subsequent visits).

- We will induce a small electrical current in your brain by the use of an electromagnetic coil and measure the response through your spinal cord to your bladder/bowels. (The sensation is described as 'unusual' unusual' as you may the sensation of involuntary muscle movement particularly in the face, however, it is not painful and has been used on healthy volunteers). This procedure is called *Transcranial Magnetic Stimulation.*

The purpose of these investigations is to develop a procedure by which we can determine what residual nerve activity remains between the brain and the bladder/bowel after your spinal cord injury. If your injury is very recent then we will be able to determine the nerve activity prior to your corrective spinal surgery and post surgery to ascertain whether our method of assessment is sensitive enough to pick up any nerve regeneration that might take place post spinal correction surgery.

A description of the protocol for the investigation is shown below, each visit will last for approximately 4 hours. At this stage we do not know exactly how many times we would like to repeat this experiment, but it is likely to be not more than three times. However, it is totally up to you how many times you feel you wish to undertake the procedures.

Prior to each visit we will ask you to stop taking any anti-cholinergic (bladder suppressants) medication you may be on.

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Assessment and subsequent visits

We will need to carry out urodynamics tests, similar to those, which you may have previously had. This will ascertain your current bladder function. We will give you an antibiotic injection or tablets, as there is a small risk (1-2%) of you developing a urine infection.

We will carry out assessments of sphincter activity using a technique called *Dorsal Penile Nerve Stimulation (DPN).*

We will then monitor the response of your sphincters to an increasingly full bladder and will stop at regular intervals to apply DPN stimulation. During these intervals we will ask you to squeeze or imagine squeezing your anal sphincter or pelvic floor. This allows us to assess any remaining brain-spinal nerve pathways.

If you agree, on a second visit we will then repeat the above tests but incorporate *Transcranial Magnetic Stimulation* (TMS). This will give us information on the nerve pathways between your brain, spinal cord and bladder, bowel and sphincters. Each visit will take approximately 4 hours and we will reimburse you for any travel expenses.

You are free to withdraw from this study at any time, without this affecting the care that you receive. All information will be treated confidentially. The study results may be published in scientific journals. You will not be identified in person.

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PUBLICATIONS AND PRESENTATIONS AND AWARDS

Peer Reviewed Papers

Michael D. Craggs, **Amirthe Vernie Balasubramaniam**, Eric A.L. Chung, Anton V. Emmanuel (2006) Aberrant reflexes and function of the pelvic organs following spinal cord injury in man *Autonomic Neuroscience: Basic and Clinical* 126- 127 355 - 370

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